SEP 14 1925
Medical Lib

VOL. CLXX, No. 3 SEPTEMBER, 1925 No. 642

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

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ESTABLISHED 1820

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Philadelphia LEA & FEBIGER New York

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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

SEPTEMBER, 1925

ORIGINAL ARTICLES.

ADIPOSITY AND OTHER ETIOLOGIC FACTORS IN DIABETES MELLITUS.*

By James M. Anders, M.D.,

and

H. Leon Jameson, M.D.,

Philadelphia.

This contribution to the etiology, incidence and death-rate of diabetes mellitus, is based principally upon the mortality statistics of Philadelphia for the last forty-five years, and also figures derived from cases of adiposity and diabetes personally observed. It may be fairly assumed that increase in the death-rate indicates an increase in the incidence of diabetes, since it has been conclusively shown by Cabot[1] that the percentage of accuracy of statement in respect to the diagnosis of this disease is high.

It is to be recollected, however, that notwithstanding the earlier detection of glycosuria and the greater frequency of blood-sugar determinations in symptomless cases, as well as closer and more enlightened attention to their dietetic supervision, in recent years the mortality-rate had been, according to the results of our statistical studies, rising steadily until the introduction of insulin as a remedy. This is shown graphically by Chart I (see below) which is based on the mortality figures for Philadelphia for the last forty-five years, or from 1880 to 1924 inclusive.

Tracing (*A*) shows the rise in the deaths from diabetes mellitus for practically the same period of time for each 100,000 of the population, or from 3.53 per cent to 17.6 per cent, while (*B*) represents the decline in the death-rate from all causes per 1000 of the popula-

* Read before the Association of American Physicians, May 5, 1925.

tion of this city during that period, or from 21.14 per cent to 12.95 per cent. Joslin[2] claims that the patients seen at the present day are older and represent a milder type of the disease, which of itself indicates "not so much new cases as a greater zeal displayed in their discovery." The various agencies that have caused the fall in the general death-rate in Philadelphia and other large cities are too well known to require a detailed statement of the facts connected therewith. Suffice to say that the reduction has been most notable in certain specific instances, for example, the communicable diseases of childhood, infantile complaints and such infectious diseases of adult life as typhoid fever, tuberculosis, malaria and yellow fever.

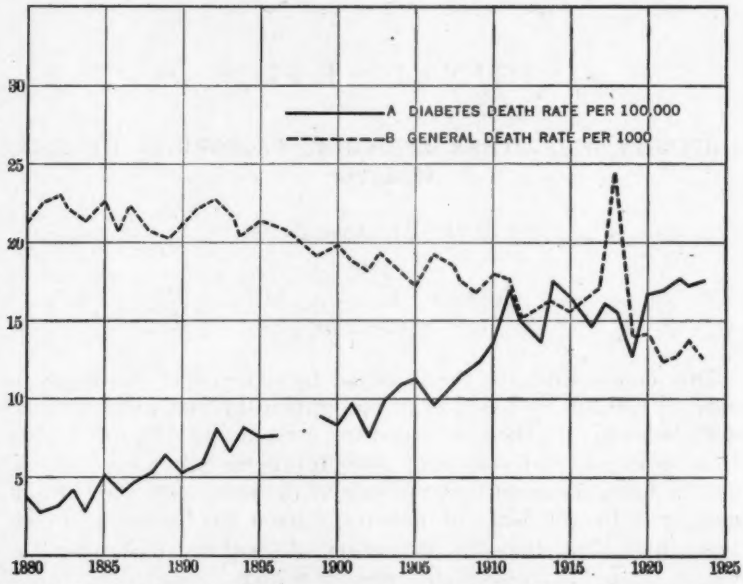

CHART I.—The break in the continuity of tracing (A) is due to the fact that no data were available for the years 1897 and 1898.

Insulin has checked the further rise in the death-rate during the last half of 1923 and during 1924 in Philadelphia (see Chart I). It is claimed by the Metropolitan Life Insurance Company[3] that a reduction in the death-rate from diabetes among their industrial policy holders during the last half of 1923 and the first quarter of 1924 as the result of the extensive use of insulin during that period has occurred. As shown by Foster[4] treatment of diabetic coma with insulin often causes consciousness to return. It is quite probable that the case-mortality percentage of diabetes will be considerably reduced by the widespread and more judicious use of insulin in the future, through an indefinite postponement of the fatal issue and possible cures in functional cases. Admitting the truth

of these statements, the influence of insulin may be disregarded as affecting our mortality-data, covering a period of forty-three years ending with June 30, 1923.

Emerson and Larimore[5] give as a reason for studying the deaths from this disease "the considerable shift in relative importance numerically of the leading causes of death which has dropped tuberculosis from first to fourth place and has brought diabetes up to tenth place." It is of interest to note here that in the Registration Area of the United States in 1920, diabetes appears in the twelfth place. Similar mortality data for the year 1923 in Philadelphia are presented in Table I. These, it will be noted, also assign diabetes to twelfth place (see Table I).

TABLE I.—RELATIVE RATING OF THE LEADING CAUSES OF DEATH IN PHILADELPHIA (1923).

Disease.	Total.
1. Heart disease	4162
2. Pneumonias (lobar and broncho)	3260
3. Acute and chronic nephritis	2375
4. Cancer	2234
5. Tuberculosis of lungs	1867
6. Congenital debility and malformations	1156
7. Diseases of arteries	813
8. Apoplexy	753
9. Diarrhea and enteritis (under two years)	571
10. Influenza	425
11. Injuries by falls	337
12. Diabetes	335
13. Appendicitis and typhlitis	328
14. Syphilis	323
15. Injuries by automobiles	304
16. Diphtheria	270
17. Embolism and thrombosis	254
18. Measles	223

There has been a decided shift in the numerical rating of diabetes in Philadelphia in recent times; for instance, in 1913, or ten years prior to having reached the twelfth place, it occupied twenty-second place. It is clear that while there was a decided increase in the mortality-rate of diabetes in Philadelphia until 1923, it was not quite as great as in New York City. We may account for New York's higher death-rate by the higher percentage of Jews in that city as compared with Philadelphia. Table II further emphasizes the higher average mortality-rate for New York as compared with Philadelphia.

TABLE II.—AVERAGE DEATH-RATE FROM DIABETES PER 100,000 FOR BOTH PHILADELPHIA AND NEW YORK FOR FORTY-FIVE YEARS ACCORDING TO FIVE YEAR PERIODS.

	1880 to 1884.	1885 to 1889.	1890 to 1894.	1895 to 1899.	1900 to 1904.	1905 to 1909.	1910 to 1914.	1915 to 1919.	1920 to 1924.
Philadelphia	3.4	5.1	6.6	8.0	9.1	11.2	15.5	15.0	17.0
New York	4.1	6.4	8.0	9.8	12.3	14.8	17.0	19.8	21.4

The death-rate of diabetes mellitus in Philadelphia during forty-five years according to age groups and sex is shown in Table III. The steady rise in the mortality-rate among both sexes during many years and especially the phenomenal rise among females during the last fifteen years are shown by both Table No. III and Chart No. II (see below).

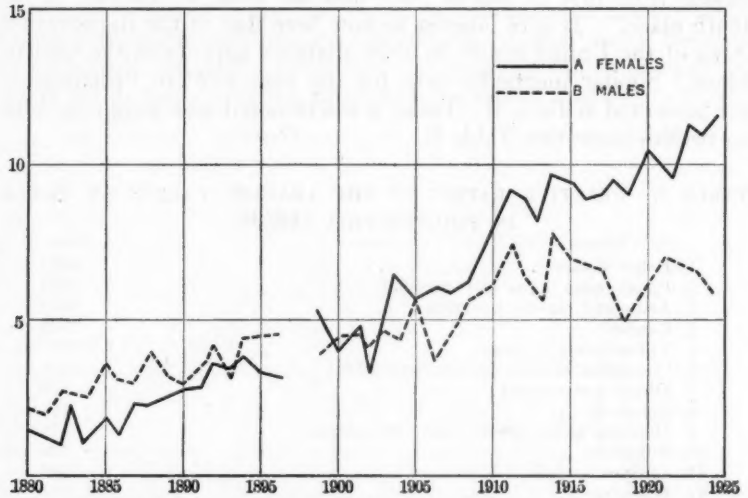

CHART II.—The interruptions in continuity of tracings (A) and (B) are due to the fact that no figures for 1897 and 1898 were available.

Emerson and Larimore found on comparing the experience of the "Registration States and of New York City by five-year-age groups for 1920, that after the age of forty, women show higher diabetes death-rates, except that males in the Registration Area over eighty years of age again take the lead." In New York City, while the proportion of all diabetic deaths has remained about stationary under twenty years of age for upwards of fifty years, the preponderance for that period occurred among the males. While our own collective investigations do not indicate the sex in relation to age groups, they show only a slight increase in the mortality-rate between birth and twenty years of age during forty-five years in Philadelphia.

A glance at Table III will show that the rise in the diabetes death-rate is beyond both the increase in the general population and the total deaths from all causes. Again, the death-rate per 100,000 from this disease was more than five times greater in 1924 than in 1880 in Philadelphia. For example, when the column showing the total diabetes deaths for this city is consulted, it will be seen that the mortality in 1924 exceeded ten times that of 1880, while the population for the former year was only two and a half times that of the latter. The increase in the death-rate and the incidence of

diabetes has been unparalleled by any other affection, if we except severe epidemics, such as the sudden and widespread appearance of malignant influenza and the like.

TABLE III.—DEATHS AND DEATH-RATES, ALL CAUSES, AND FROM DIABETES, FROM 1880 TO 1924.

Year.	Population.	Total deaths all causes.	Crude death-rate per 1000.	Diabetes deaths.			Diabetes death-rate per 100,000.	Percentage diabetes deaths of all deaths.	Age groups.			
				Total.	Male.	Female.			0 to 19.	20 to 39.	40 to 59.	60 +.
1880	848,835	17,942	21.14	30	19	11	3.53	0.167	3	12	6	9
1881	868,814	19,761	22.74	25	15	10	2.88	0.126	.	9	12	4
1882	888,793	20,293	22.83	28	20	8	3.22	0.137	3	7	8	10
1883	908,772	20,338	22.38	39	21	18	4.29	0.191	4	7	13	15
1884	928,751	20,320	21.88	29	21	8	3.12	0.191	3	8	11	7
1885	948,730	21,694	22.87	48	33	15	5.05	0.221	2	12	16	18
1886	968,709	20,349	21.01	42	31	11	4.33	0.206	3	11	15	13
1887	988,689	22,194	22.45	49	29	20	4.95	0.221	4	8	19	18
1888	1,008,669	20,750	20.57	52	36	16	5.15	0.251	3	11	20	18
1889	1,028,649	21,038	20.45	64	33	31	6.21	0.304	9	13	18	24
1890	1,049,020	22,273	21.23	55	28	27	5.24	0.247	1	14	20	20
1891	1,073,693	24,003	22.36	64	35	29	5.95	0.267	4	10	28	22
1892	1,098,366	25,033	22.79	84	45	39	7.65	0.332	5	14	22	43
1893	1,123,039	24,442	21.76	72	35	37	6.41	0.295	4	15	24	29
1894	1,147,712	23,500	20.48	92	48	44	8.01	0.391	5	18	30	39
1895	1,172,385	24,634	21.01	92	52	40	7.85	0.373	8	17	22	45
1896	1,197,038	24,782	20.70	92	53	39	7.66	0.371	7	7	39	39
1897	1,221,711	23,505	19.24									
1898	1,246,385	24,614	19.75									
1899	1,271,059	24,534	19.30	114	48	66	8.97	0.465	7	22	34	51
1900	1,295,852	25,695	19.83	109	57	52	8.41	0.424	7	15	38	49
1901	1,312,706	24,659	18.66	124	60	64	9.44	0.503	5	25	36	58
1902	1,347,560	24,374	18.09	98	54	44	7.27	0.402	6	12	40	40
1903	1,373,414	26,725	19.46	133	65	68	9.69	0.498	5	23	49	53
1904	1,399,268	25,971	18.56	152	65	87	10.86	0.585	7	17	59	69
1905	1,425,122	24,807	17.41	161	81	80	11.30	0.649	8	16	60	77
1906	1,450,976	27,768	19.14	140	52	88	9.65	0.504	5	17	56	62
1907	1,476,830	27,476	18.61	157	70	87	10.62	0.571	10	28	51	68
1908	1,502,685	25,926	17.25	178	84	94	11.84	0.687	9	23	63	83
1909	1,528,540	25,029	16.37	196	90	106	12.82	0.783	8	19	70	99
1910	1,554,902	27,045	17.39	220	96	124	14.15	0.813	8	26	78	108
1911	1,583,190	27,276	17.23	264	118	146	16.68	0.968	6	23	97	138
1912	1,611,478	24,513	15.21	245	100	145	15.20	0.999	10	25	102	108
1913	1,639,766	25,612	15.62	230	94	136	14.02	0.898	9	18	86	117
1914	1,668,054	26,918	16.14	290	128	162	17.39	1.077	7	41	100	142
1915	1,696,342	26,287	15.50	278	118	160	16.39	1.058	12	21	90	155
1916	1,724,630	27,621	16.02	256	104	152	14.84	0.927	6	27	101	122
1917	1,753,058	29,681	16.93	273	115	158	15.57	0.920	7	39	96	131
1918	1,781,346	42,933	24.10	275	106	169	15.44	0.641	8	30	117	120
1919	1,809,635	25,946	14.34	233	88	145	12.87	0.898	14	26	92	101
1020	1,837,924	26,516	14.43	295	106	189	16.05	1.112	10	32	97	156
1921	1,866,212	23,704	12.70	310	129	181	16.61	1.307	12	35	103	160
1922	1,894,500	25,103	13.25	337	126	211	17.78	1.342	18	29	135	155
1923	1,922,788	26,654	13.86	335	124	211	17.42	1.256	5	35	139	156
1924	1,951,076	25,280	12.95	345	116	229	17.6	1.365	11	26	120	188

The differences between the deaths of the sexes on comparing individual and groups of years are interesting. For example, from 1880 to 1902 the diabetic deaths among males exceeded those among females in Philadelphia with two exceptions, whereas from 1903 until 1924 inclusive the reverse obtained. It will be observed that in recent years the excess of deaths among the females progressively increased until the sex ratio reached nearly 2 to 1 in favor of the latter sex. Emerson and Larimore state that at the ages of forty-five and over for New York, the proportion of all diabetes deaths has increased and those of females at a greater rate than those of males. This statement agrees with the results of our observations for Philadelphia as stated above. The precise causative factors which have brought about the rising death-rate of diabetes during the last half century remain in great measure unknown. It has been shown, however, that in this period of time the food intake has gradually increased and also that the amount used has passed far beyond human needs. Emerson and Larimore give charts and tables which indicate that rises and falls in the sugar consumption "are followed with fair regularity within a few months by similar rises and falls in the death-rates from diabetes, the changes during the period of the World War being particularly striking."

The main purpose of this article is to show the etiological relationship of obesity to diabetes (see Table IV). Many allied questions, however, have arisen in connection with the consideration of this subject and some of these have been statistically investigated and discussed. Fisher and Fisk[6] have shown definitely, by tables compiled from medico-actuarial statistics of life insurance companies, that the effect of overweight on mortality among healthy individuals is considerable. If this be true, and added to our knowledge of the predisposing causes of diabetes, it would be wisdom on the part of the diabetics to avoid overweight.

Certain generally accepted facts appertaining to predisposition to diabetes have not been given any detailed consideration. The greater hazard of diabetes among the Jews as compared with Gentiles, however, we believe, received further significant confirmation from the results of our studies.

The importance of advancing our knowledge of the predisposing causes of a widely prevalent disease such as diabetes mellitus, can hardly be exaggerated. The statistical inquiry into the predisposing influence of obesity in diabetes mellitus, which we have conducted has been limited exclusively to cases personally observed, or a total of 1306 cases of the former condition, and 145 of the latter. As shown by a glance at Table IV, our studies were established on a few simple lines and the chief results obtained, indicated thereon, are largely self explanatory.

According to our figures, the average percentage of overweight is higher among females than males, and while this is true of both

Gentiles and Jews (see Table IV), the latter race shows the higher average percentage of overweight. It would appear, therefore, that the more marked average adiposity among females, brought about, as has been pointed out, by a larger sugar consumption and more sedentary lives, is the cause of the greater incidence of diabetes in them. It may be a matter of surprise, therefore, that Table IV does not show a preponderance of cases of adiposity among females over males, but only a higher average percentage of overweight as already stated.

TABLE IV.

	Total number of patients.	Total number of obese.	Percentage of obese.	Average percentage of overweight of all obese.	Total number of diabetics.	Percentage of diabetes.	Average percentage of overweight in diabetics.
Gentiles:							
Male	2913	606	20.80	21.84	57	1.96	19.88
Female	2927	488	16.67	27.02	55	1.88	23.20
Total	5840	1094	18.73	25.33	112	1.92	21.62
Jews:							
Male	652	113	17.33	24.55	18	2.91	25.07
Female	598	99	16.56	29.71	15	2.51	31.22
	1250	212	16.96	26.44	33	2.71	27.55

Table V confirms in a striking manner the fact that the incidence of diabetes among obese Jews is higher than among obese Gentiles, the ratio being as 12 to 8 in favor of the former. While "more Gentiles than Jews are underweight and more Jews than Gentiles overweight" (Joslin), the higher incidence among Jews may be dependent solely, as Joslin contends, upon a greater average percentage of overweight as shown by the figures just given. It would appear to us, however, that the difference in the average percentage of overweight is not great enough to account for this discrepancy in incidence. Table V also shows that 26 cases of diabetes occurred in persons not above the normal weight.

TABLE V.

	Gentiles.	Jews.
Total number of obese cases	1094	212
Average percentage overweight	25.33	26.44
Number of diabetics in obese cases	92	27
Percentage of obese cases with diabetes	8.4	12.74
Total diabetics normal or underweight	20	6
Percentage of total diabetics underweight	16.96	18.18
Percentage of totals with diabetes underweight	1.80	2.75

Again, Table VI covers the same points for a twenty-year period, from 1910 to 1924 inclusive and tells much the same story.

TABLE VI.—1910 TO 1924.

	Cases of adiposity.	Male.	Female.	Average per cent of overweights. Male.	Female.
Gentiles . . .	786	451	335	19.98	25.64
Jews	173	96	77	21.78	26.95
Total . . .	959	547	412		

TABLE VII.—1915 TO 1924.

	Cases of adiposity.	Male.	Female.	Average per cent of overweights. Male.	Female.
Gentiles . . .	484	246	238	22.12	26.55
Jews	115	54	61	22.42	28.23
Total . . .	599	300	299		

In Table VII, the figures for the last decade, namely from 1915 to 1924 inclusive, show clearly that the increase in the average percentage of overweight among females in comparison with males is maintained. There is a disproportionate rise in the number of female diabetics, and, in the case of the Jews, they outnumber the males.

TABLE VIII.—1915 TO 1919.

	Cases of adiposity.	Male.	Female.	Average per cent of overweights. Male.	Female.
Gentiles . . .	228	140	88	23.46	27.32
Jews	47	23	24	23.09	31.25
Total . . .	275	163	112		

The figures in Tables VIII and IX indicate that during the decade last passed and more particularly during the latter half of that period (see Table IX), a striking increase in obese females as compared with males occurred. This fact proves that adiposity is a dominant predisposing factor. Our statistics for Philadelphia (presented in Table III) indicate a similar sudden, marked rise in the death-rate among females in recent years. True it is that the mortality from diabetes mellitus among males has also been rising, but not by any means to the same extent as among females. It is of much interest to note that in Table IX, unlike previous ones, the females show a preponderance of adiposity in the grand total and also for both Gentiles and Jews.

TABLE IX.—1920 TO 1924.

	Cases of adiposity.	Male.	Female.	Average per cent of overweights. Male.	Female.
Gentiles . . .	257	104	153	20.03	26.14
Jews	66	28	38	22.35	26.79
Total . . .	323	132	191		

That the significant, decisive rise in the diabetes death-rate and incidence among women is not wholly attributable to the greater adiposity of that sex can be, we believe, proven. For example, when the figures of Table VIII are compared with those of Table IX, it will be seen that the average percentage of overweight among women for the five-year period, 1915 to 1919 inclusive, is greater than that of the next period of the same duration, or 1920 to 1924 inclusive. It is obvious, therefore, that obesity is not the sole causative influence in bringing about the far heavier incidence among women during the last five years. Neither do we believe that the more sedentary lives of females than males alone accounts for the far greater percentage of cases of diabetes among the former sex during that time. While adiposity does not per se explain the marked rise in the prevalence of diabetes in the female during the last five or six years, it is unquestionably the most potent, single predisposing factor in this disease. The greater frequency of diabetes in persons over forty years of age is shown by Tables X and XI.

TABLE X.

	1905–1914				1915–1924.			
	Total number of diabetics.		Number of diabetics over forty years of age.		Total number of diabetics.		Number of diabetics over forty years of age.	
	Male.	Female.	Male.	Female.	Male.	Female.	Male.	Female.
Gentiles . .	24	18	20	14	27	40	23	31
Jews . . .	10	3	5	2	8	12	6	10

TABLE XI.—DIABETICS—AGE GROUPS BY DECADES.

	Gentiles.		Jews.	
Age	Male.	Female.	Male.	Female.
1 to 9	..	..	..	..
10 to 19	..	2		
20 to 29	..	2	..	2
30 to 39	7	9	8	1
40 to 49	16	13	3	5
50 to 59	20	20	5	5
60 to 69	12	9	2	2
70 to 79	2			
Total	57	55	18	15

In emphasizing the importance of special preventive measures in the future, Joslin states that wherever sanitary science is at its best, the morbidity of diabetes will be at its highest, because "the disease is fifteen times as common among those over forty years of age as among those under forty years, and the percentage of Americans today over forty is rapidly increasing." While these facts help us to explain the increasing incidence of diabetes in general, they do not explain the much greater rise in frequency of occurrence among females in recent years, since their expectation of life shows no

striking figures over those of males. It is well known that the chief cause of adiposity is the ingestion of foods containing a large percentage of carbohydrates, as sweets, soft drinks, candies and the like.

According to our studies, lack of physical effort is a strong predisposing influence. Heredity also plays a role in from 20 to 25 per cent of the cases. It is conceivable that the nerve strain occasioned by the recent World War fell more heavily on the female than the male sex. It should be recollected, however, that the rise in incidence, as shown by the figures for Philadelphia (Table III) as well as those based on cases personally observed, had been greater among women than men during the war and prewar years, although less pronounced than since that struggle ended. While the strain of the war may have been a potent predisposing factor, it does not seem to us to fully explain the unusually and rapidly increasing prevalence of this disease among women in recent years.

Again, according to our statistical investigations none of the hitherto known predisposing influences either singly or in combination, explains the phenomenal increase in incidence of diabetes mellitus among females during the last five or six years; and it is obvious that the determination of its cause would have an important bearing on the prophylactic treatment of the disease.

Emerson ascribes the increasing diabetes incidence in this country to a lessened per capita use of meat and an increased per capita consumption of sugar, cereals, milk, vegetables and fruits. He also supports the contention of Allen by statistical evidence, that much diabetes is due to a fatigue of the function of carbohydrate tolerance by an attempt to assimilate a diet which overstrains this function.

That the greater prevalence of diabetes has been encouraged by changes in food habits is an assumption further supported by a considerable amount of evidence. For example, Taylor[7] points out that not only an increased per capita sugar consumption, but also that of fruits has taken place coincident with a reduction of the per capita use of meats. Riesman[8] holds that the cause of the increase of diabetes is the greater per capita sugar consumption coupled with the increase of sedentary habits among most classes of people. The habitual ingestion of too much food causing a gain of weight is a potent factor. The foregoing views, however, fail to take account of the fact that such dietetic changes have most probably affected males as well as females, although possibly to a less extent.

It is well known that certain diseases other than diabetes have similar characteristics, for instance, exophthalmic goiter, which has shown an increased frequency of occurrence during recent years (although less marked than diabetes), and a higher incidence among females than males. In both we are concerned with disorders of endocrine function.

It is known that extirpation of the pancreas is invariably followed by all of the clinical indications of diabetes mellitus and also hyperglycemia. That the influence of the pancreas in carbohydrate metabolism is due to an internal secretion, the product of the islands of Langerhans, is a statement which will command universal agreement. The increased tolerance for carbohydrates often acquired by diabetics as the result of fasting, leaves little room for doubting that the disease of the pancreas giving rise to diabetes is often a functional one during its earlier stages at least. It is equally clear that while the pancreas supplies something which normally enables the tissues to utilize sugar, there would seem to be a number of agencies capable of interfering with this function. The significance of these factors, which induce fatigue of the function of carbohydrate tolerance, however, is not definitely known.

Summary. From these statistical studies, it would appear that the death-rate of diabetes in Philadelphia had been increasing steadily until checked by the use of insulin about the middle of 1923, and that its incidence in patients under our personal observation, has been increasing steadily up to the end of 1924 among females. Whereas in 1913, the numerical rating of diabetes as a cause of death assigned it to twenty-second place, ten years later or in 1923, it occupied twelfth place, corresponding with what was found in the Registration Area of the United States and in New York in 1920. According to our findings after the age of forty, women showed a decidedly higher diabetic death-rate and heavier incidence than men during the past two decades, while for the like preceding period, the preponderance of deaths from this complaint occurred among males. This change in the influence of the sexes upon mortality-rate of diabetes is one of the most interesting facts in medicine and, moreover, no satisfactory explanation can be offered for it. In our series of 1306 cases of adiposity, which includes 119 cases of diabetes, this sex relationship was also noted with respect to the incidence of the disease. The excess of deaths among females has progressively increased in Philadelphia in recent years until the sex ratio reached approximately 2 to 1 in favor of females.

The predominant effect of adiposity as a predisposing cause of diabetes is clearly indicated by the accompanying tables, although it is to be recollected that only 1 in 12 obese subjects develop diabetes among Gentiles, and 1 out of every 8 among Jews. Whether the higher ratio among the Jewish race is owing to greater susceptibility to the disease or a relatively greater degree of overweight alone, as Joslin believes, is perhaps still an unsettled question. We believe that the phenomenal rise in the diabetes death-rate and incidence among women in recent years, as shown by the statistical studies of Emerson and Larimore and also our own figures, is not due solely to their greater and more general adiposity. For example, it is shown by our statistics that the cases of diabetes have multiplied

themselves five times since 1880; but it cannot be justly claimed that overweight has increased in degree to a like extent. Again, on comparing Table VIII with Table IX this statement is strongly corroborated. Finally, in 18 per cent of our cases of diabetes, the disease occurred in persons of normal or even subnormal weight.

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PROBLEMS IN THE DIAGNOSIS AND TREATMENT OF INFILTRATING TUMORS OF THE CEREBRAL HEMISPHERES, WITH REMARKS ON A NEW SURGICAL PROCEDURE.*

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In spite of the advances in the surgery of the brain—advances which may be called remarkable and in which the part played by American neurosurgeons may be pointed to with justifiable pride—little progress has been made in the surgical treatment of infiltrating tumors of the cerebral hemispheres. In a large number of the patients, the exposure of the brain and the tumor, after a large osteoplastic bone flap has been turned down, reveals a condition of affairs which is beyond remedy by surgical means.

In those forms of infiltrating tumor in which, for reasons not yet well understood, the neoplasm has undergone degenerative changes with the formation of a small or large cystic cavity lined by a thin or thick wall of gliomatous tissue, the outlook for therapy is a little better. Some of these cystic gliomas can be incised, their contents evacuated, knobs or masses of tumor tissue excised, the walls of the cyst cauterized with Zenker's solution or some other

*Read by title at the meeting of the American Neurological Association, Washington, D. C., May, 1925.

fixative, and the patients benefited and sometimes relieved for many years.

Occasionally, as in the case illustrated in Figs. 1 and 2, a pedunculated tumor lies within a cyst cavity, and the mass together with the thin wall of the cyst can be radically extirpated.

In still other patients, the cyst cavity can be emptied after it has been punctured with a needle, and the contents can be evacuated at regular intervals by a simple puncture of the cystic cavity. (Figs. 3 and 4.)

Some of these cystic gliomas run a slow course after the fluid contents have been removed: the patient is relieved of most or even of all of his symptoms for one to two years or longer.

The results of attempts at radical excision of solid infiltrating growths have mostly been disastrous failures. In rare instances, the growth is small and in a location where excision is possible; but in most of the patients, the growth is so large that it cannot be completely excised and even if a radical excision be possible, extensive loss of function is certain to follow.

A few years ago, I carefully studied all of the brains with infiltrating tumors in our collection, and found only a single specimen in which the growth was small enough or so situated that its complete removal would have been possible. The results of extensive excision of entire lobes of the cerebrum have not been satisfactory even in the hands of the most enthusiastic advocate of such radical resection of the brain, and the operation is rarely a justifiable one.

Occasionally, in a deeply subcortical infiltrating neoplasm which has grown toward the surface of the brain, the superficial portion of the growth is not infiltrating but has well-defined margins. In these patients the superficial part of the growth can be peeled out of the cortex in the same way as is done with an endothelioma, but when the deeper part of the growth is reached, it is found to infiltrate the subcortical tissues, so that only the superficial part of the growth can be removed. After the excision of the superficial part of the tumor, there may be, for a time, considerable improvement, but in most instances the improvement is not as much due to the partial excision of the growth as to the decompressive effect of the entire surgical procedure.

The largest number of fatalities after operations for brain tumor occurs in patients with surgically irremediable subcortical infiltrating growths, although the dangers of exploratory operations have been definitely diminished by the use of local instead of general anesthesia.

If it were possible to exclude from the category of cases which require major operative interference many of the hopeless infiltrating growths, the results of brain tumor surgery would be much improved.

Consider how much would be gained if such a selection of cases would be possible. How many patients and their families would be saved from the stress and strain of the surgical procedure? How

great would be the economy of time and energy? It is a great waste of energy for the surgeon to perform an operation which often requires several hours, only to find a surgically irremediable condition. Likewise, the time of assistants and of nurses and the amount of surgical materials used for such an operation are economically far in excess of what is accomplished by the surgical procedure.

If it were possible to make the diagnosis of an infiltrating tumor very early when the growth is still a very small one, and further, if one could determine before hand that the small infiltrating neoplasm was entirely in or near the cortex, something could perhaps be done by surgery. Such a consummation, devoutedly to be wished for, is as yet impossible. I am therefore convinced that the next advance will come from the better recognition of, and discrimination between, meningeal growths on the one hand and subcortical infiltrating growths on the other.

The entire problem resolves itself into the question: How often will it be possible to make the diagnosis "subcortical infiltrating tumor" before the operation with sufficient certainty that a major exploratory operation can be avoided?

In attempting to answer this question, it is logical to speak first of the neurological symptoms and signs of subcortical growths, and the possibility of a diagnosis being so certain that exploratory operation can be refused. In some patients, the diagnosis can be made with certainty, in others it can be suspected, but in very many cases the patient is given the benefit of the doubt, and a major exploratory craniotomy is advised. No doubt the time will come when the signs and symptoms of subcortical infiltrating growths will be much better understood and the clinical picture of this type of growth more clearly defined, so that a positive diagnosis will be made more often than is possible today.

The purpose of this paper is not to discuss the purely neurological aspects of the problem, but to consider the part that the neurosurgeon should take to lessen the number of exploratory operations.

1. **The Study of the Roentgenograms of Patients in Whom Air has been Injected into the Ventricular Cavities.** The injection of air into the ventricles and ventriculography, in spite of the dangers, is of value not only for the localization of otherwise unlocalizable growths, but also for the differentiation of subcortical from superficial neoplastic disease.

For the past year, Dr. Silbert and I have been making casts of the lateral and third ventricles of the brains of patients who have died from tumors, have studied the finer changes in the shape and size of the lateral ventricles, and have compared the actual casts of the ventricles with the ventriculograms of the patients taken before death. We then correlated the data obtained with the size, shape and location of the tumor, and finally attempted to explain

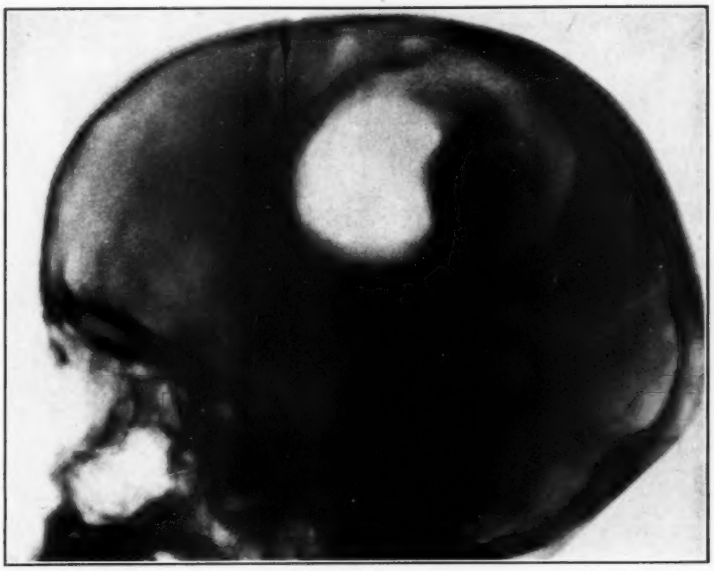


FIG. 1.—L. L., Neurological Institute. A pedunculated tumor within the cavity of a gliomatous cyst shown by pneumography—lateral view.

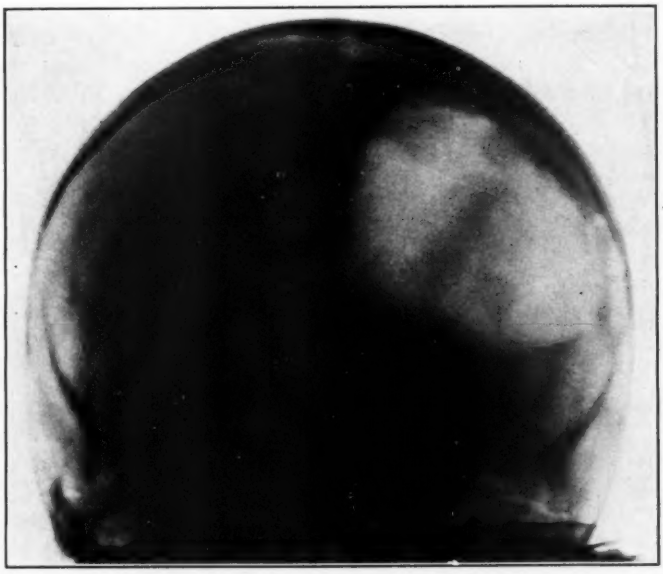


FIG. 2.—L. L., Neurological Institute. A pedunculated tumor within the cavity of a gliomatous cyst shown by pneumography—antero-posterior view.

FIG 3.—P. H., Neurological Institute. An irregular shaped cavity of a gliomatous cyst shown by pneumography—lateral view.

FIG. 4.—P. H., Neurological Institute. An irregular shaped cavity of a gliomatous cyst shown by pneumography—antero-posterior view.

the objective neurological disturbances including the papilledema in each eye by the comparison of the changes in the ventricles, the size and location of the growth and the changes in the size of the two cerebral hemispheres.

These investigations have taught us a number of valuable facts regarding the mechanical effects of supratentorial growths and have led us to more fully appreciate the changes seen in the ventriculogram. Our studies are far from concluded, but a preliminary report will be published in the near future.

As is well known, superficial growths—especially the endotheliomata—may deform one or both lateral ventricles. A meningeal growth over one frontal lobe may collapse part of one or both anterior horns; one over an occipital lobe or on the under surface of a temporal lobe may collapse the posterior or inferior horn of the homolateral lateral ventricle, but it is more rare for such a meningeal growth to cause much distention of the opposite lateral ventricle or of that of the same side.

If an endothelioma is so placed as to make pressure upon one or both foramina of Monro sufficient to occlude one or both of them, distention of one or both lateral ventricles may follow and even part of or the entire contralateral ventricle may be shown to be dilated. This is, however, relatively very infrequent. Subcortical growths, on the other hand, both on account of the tumor and of the hyperplasia of the lobe, usually cause a well-marked dilatation and often a dislocation of some part of the contralateral ventricle. Therefore, in a suspected hemisphere growth, a marked dilatation of the contralateral ventricle makes it more probable that the growth is subcortical and therefore infiltrating.

Furthermore, there is, as should be the case, a definite relation between the location of the tumor, the amount of distention of the anterior, posterior and inferior horns of the contralateral ventricle, the degree of fundus changes in each eye and the disturbances in function on both sides of the body. The details of all of these changes will be given in full when Dr. Silbert and I publish the results of our studies, but I have made mention of this fact only in order to remind you that the value of ventriculography is not only to localize an otherwise unlocalizable growth, but also to distinguish between meningiomas and subcortical tumors. When the time will come, as it surely will, that we shall be able to obtain stereoscopic roentgenograms of the ventricular system after the injection into the ventricles of a nonirritating fluid which is impermeable to the roentgen-ray, instead of air, the information we shall be able to obtain from ventriculograms will be much greater than it is today. We have been investigating this problem for many years, and, no doubt, others are making a search for a fluid that can be injected into the ventricular cavities for this purpose.

2. **Calcification,** visible on the roentgen-ray films occurs in a small number of subcortical infiltrating growths, and the appearance of this calcification is very characteristic and should be recognized. Dr. C. W. Schwartz, the director of the Roentgenological Laboratory of the New York Neurological Institute, and I have been carefully studying the changes visible in the roentgenograms of the skulls of these patients. The shadows are usually very slight and can often only be recognized on stereoscopic examination. The calcification is usually rather diffuse without distinct borders, and irregular in shape and outline. Its appearance is different from that of calcified cysts of the pituitary body, or of the calcification seen in so many craniopharyngeal pouch tumors. It has a different appearance from the calcification of the falx cerebri or other parts of the meninges, so often seen on roentgen-ray films, and the stereoscopic examination of the films shows that the shadow seen is within the substance of the one or the other hemisphere.

3. **The Surgical Procedures Recommended in Suspected Subcortical Hemisphere Tumors.** The main object of this paper is to recommend as a regular surgical procedure, one that differs from that ordinarily performed by the neurosurgeon.

In most of our operations for supratentorial infiltrating growths, we have been accustomed to turn down a large osteoplastic flap in order to expose and explore the part of the brain in which the tumor is presumably located. The growth is found either infiltrating the cortex, or is demonstrated to be subcortical by puncture or by actual incision of the exposed brain, or the puncture of the brain fails to demonstrate any pathology. In the majority of these patients the operation is concluded with the aspiration of a cyst cavity, the injection of air into a cyst cavity in order to determine the size and extent of the cyst by roentgen-ray, or if the growth is not cystic, by the removal of a specimen, by the making of a subtemporal decompressive opening, or by the removal of part of the bone flap overlying the growth for the purpose of later roentgen-ray or radium therapy.

Instead of this major operative procedure, and it is a major surgical interference, even if done under local anesthesia, I suggest that the following method be adopted as the regular procedure: Under local anesthesia, an incision is made through the scalp in a location and direction that it may form part of the line of incision for the outlining of an osteoplastic flap, if that be later required. Through this primary short incision, a button of bone is removed with the trephine and a small incision, sufficient to permit the passage of a blunt brain puncture needle, is made in the dura.

If no tumor is found directly under the opening in the dura, the subdural space is carefully explored in various directions with a broad flat probe made of German silver and bent so that it can be passed underneath the dura. For this purpose, the blunt cannula

devised for puncture of the corpus callosum can be used. The majority of endotheliomas are adherent to the dura, have buried themselves, more or less, in the brain, and lie over the convexity of the hemispheres near one of the large venous sinuses. More rarely, the growth develops from the dura over the cribriform plate of the ethmoid, from the falx between the two hemispheres, or from the dura underneath a frontal, temporal or occipital lobe.

If a distinct, firm resistance is felt by this subdural exploration—as would occur in the presence of a meningeal tumor—then the surgeon at once proceeds to anesthetize a large area with novocain solution, to divide the scalp and to make a large osteoplastic bone flap. If no resistance is met with, the brain itself is punctured in several directions with a blunt ventricular puncture needle.

If the puncture is slowly and carefully done, slight differences in the resistance to the passage of the needle can often be appreciated and the location of the tumor determined by this means. The resistance is usually a very slight one unless intracranial tension is very high and only slight pressure is needed to advance the blunt-pointed needle after the piaärachnoid has been penetrated. If the passage of the needle is arrested by a firm resistance, there is never any doubt that a tumor or the wall of a cyst or perhaps the wall of an abscess cavity has been reached.

If a cavity which contains the typical yellow fluid which occurs in a gliomatous cyst is entered, the fluid is emptied by aspiration, and air is injected in order to obtain a roentgen picture of the cyst cavity, and the small incision in the scalp is then closed by suture and the patient sent to the roentgen-ray room.

If, on the other hand, no resistance to the passage of the blunt needle is encountered (and this is often the case), the small plugs of brain tissue obtained by aspiration are carefully preserved in formalin for histological examination, the direction in which the needle was passed and the depth to which it was inserted carefully noted, and the operation concluded for the time being.

If air has been injected into the cavity of a gliomatous cyst, stereoscopic lateral and one antero-posterior roentgen-ray films are taken.

The further course of the procedure will depend upon the results of the roentgen-ray and the laboratory examinations. After a few days, if the roentgen-ray shows that the cyst is near the cortex and does not extend deeply into the brain, an osteoplastic flap is made under local anesthesia, the size of the flap being only sufficient to expose part or all of the cyst whose exact location and size have been determined by the roentgen-ray. At this second operation, the cortex is incised down to and into the cyst, the lining wall partly or entirely excised if that be possible, or the inner wall cauterized with a fixative such as Zenker's solution.

Should the roentgen-ray show that the cyst is deeply subcortical

and especially if it extends deeply into the centrum ovale and perhaps across the midline, no second operation is attempted. The puncture of the cyst and the emptying of its contents at regular intervals will give the best results. If the cyst is of considerable size, sufficient relief of pressure is obtained by the evacuation of the cyst fluid, and only in rare instances is there need for an added subtemporal decompression.

Finally, if there is no evidence at the primary brain puncture of a cyst and if the histological examination of the tissue obtained by aspiration revealed that the growth was a glioma or its more malignant form, spongioblastoma, further operative procedures are generally useless. In the attempt to relieve headache, to save failing vision, or to prevent a rapidly progressing paralysis, we have often, primarily or secondarily, done a subtemporal decompression.

During the past two years, we have followed this plan of procedure in a number of patients with suspected subcortical brain tumors. Sometimes, as in a recent case, I have found that we were dealing with an endothelioma and then the radical operation was at once proceeded with. In another patient, operated upon a few weeks ago, we felt a resistance with the puncture needle and at once proceeded to make an osteoplastic flap, only to find that the growth was an infiltrating one in the cortex. In a number of patients, either a gliomatous cyst was demonstrated by the puncture through the trephine opening, which was near the cortex so that it was dealt with at a second operation, or it was so deeply placed and so extensive that a radical procedure was out of the question, or finally the aspiration of the brain withdrew tumor tissue from the depth and the minor operative procedure clearly showed that no satisfactory result could be expected from a major osteoplastic craniotomy.

In another paper, I shall describe the surgical procedures more in detail and shall report in full on the number of patients who have been saved from a major cranial operation; the number of instances in which the minor operation has given us all the information that could have been obtained from a major osteoplastic procedure, is rapidly increasing.

Multiple exploratory brain punctures through small openings were, many years ago, recommended for the purpose of finding an otherwise not localizable growth, but the object of the puncture here advised is to determine rather the nature and the relations of a growth which has already been localized by other means.

I am fully cognizant of the fact that, theoretically at least, a very small removable growth might not be found by the procedure here suggested—a procedure which is exactly like that now used for exploration for suspected brain abscess. The only instance in which an exploration may reveal a small tumor is one in which an endothelioma develops over part of a motor area with convulsive

attacks of the Jacksonian type, and in such a patient the indications for a primary osteoplastic craniotomy are undoubted. These cases are, in the present state of our knowledge, unusual; in most instances, the endotheliomas found and removed at operation are of considerable size.

In those patients in whom the course of the symptoms is characteristic of a cortical growth, in whom there are changes in the overlying bone (erosion of the inner table, cranial hyperostoses, localized enlargement of the diploic veins, and so forth), the diagnosis of cortical growth is so well founded that no preliminary puncture exploration such as I have described is necessary. Likewise the procedure should not be applied to growths of the pituitary, to tumors on the floor of the third ventricle or within the ventricular cavities.

If all of these cases—the probable endotheliomas, pituitary tumors, craniopharyngeal pouch and intraventricular tumors—be excluded, there remain a group of tumors of which at least 90 per cent are subcortical and infiltrating. If one considers, further, that as already mentioned, the majority of the meningeal growths are of considerable size, the conclusion is justified that the chances of missing a removable tumor by the exploration through a small opening which is here recommended, are very small. If such a meningeal growth lay between the two hemispheres or on the under surface of a frontal, temporal or occipital lobe, it would almost certainly be felt as a firm resistance when the affected lobe of the brain was punctured with the blunt needle even if no obstruction was met with by the subdural exploration.

One might argue that exploratory puncture, after a bone flap has been turned down, will allow the surgeon to puncture the brain at both the anterior and the posterior borders of the exposed dura, and therefore the chances of finding the growth should be better than through a single trephine opening.

Theoretically such an argument is well founded, but practically, if the localization of the growth has been even approximately correct, the tumor should be reached by the puncture exploration through a small opening, and this view is supported by my experience in a not inconsiderable number of cases. If the localization of the new growth was entirely incorrect, if a presumed frontal neoplasm were in reality in the posterior cranial fossa or if a growth were in the opposite hemisphere to that in which it had been localized, it would be missed as well by the puncture exploration as by the actual exposure of part of the brain by an osteoplastic procedure. Such gross diagnostic errors are, however, of rare occurrence.

If the puncture disclosed that there was a well-marked dilatation of the lateral ventricle, it would at once lead the operator to suspect that the tumor was either in the opposite side of the brain or was deeply located so as to exert its pressure upon one or both foramina

of Monro or upon the ventricular pathway caudad to this region, and the operation should then be, for the time being, concluded with the injection of air for ventriculography.

Finally, a few words should be said on the subject of the dangers of puncture of the brain in subcortical infiltrating tumors. In spite of the apparent innocuousness of puncture of the brain with the object of emptying of dilated ventricles in the course of operations for supratentorial or infratentorial disease or for the purpose of the injection of air, the number of times in which a needle is passed into the brain substance should be kept as small as possible. Undoubtedly a bloodvessel may be injured and bleeding into the brain may occasionally follow, and the possibility of hemorrhage into a tumor after the puncture of the growth must always be kept in mind. Whether or not the brain has been exposed by an osteoplastic flap, the surgeon must perform the puncture in the search for a subcortical neoplasm and the danger from a puncture through a small opening is no greater than that done after a large osteoplastic flap has been turned down.

Conclusion. The procedure that I have described is recommended with the hope and belief that it will materially diminish the number of useless major exploratory operations for supratentorial new growths, and that by this means the indications for operative interference will not only become more clearly defined but also that the results of the surgery of tumors of the brain will be improved by the exclusion of surgically hopeless intracranial disease.

LEPTOSPIROSIS ICTEROHEMORRHAGICA (WEIL'S DISEASE).

By Joseph Sailer, M.D.,
PHILADELPHIA.

With a Bacteriological Note by J. C. Small.

(From the Medical Wards and Bacteriological Laboratory of the Philadelphia General Hospital.)

On August 15, 1922, I was asked by Dr. Wm. M. Lashman, of Camden, N. J., to see with him a man aged fifty-one years. He had been sick nine days with chills, fever and pains all over the body. Jaundice has appeared early and had become steadily deeper. The pains became more severe and he felt and gave the impression of being gravely ill. The physical examination yielded little, but was nevertheless important. The jaundice was intense, involving the skin, sclera and mucous membranes. The throat, head and lungs were normal. The liver was not perceptibly enlarged nor

was anything important found in the abdomen. The reflexes were normal. There was some diffuse tenderness all over the body and the calf muscles, in particular, were exquisitely tender, so much so that he objected to a second attempt to squeeze them.

I suggested the possibility of Weil's disease and the following day Dr. Rubinstone examined the patient's blood by dark-field illumination and found a few typical parasites, although it was then the tenth day of the disease. It was my intention to have the urine also examined, but unfortunately the specimen taken to Dr. Rubinstone's office was spoiled during transmission and it could not be used. Laboratory examinations were difficult. The Wassermann test was negative, the urine contained a slight amount of albumin and bile, and the differential count of the white blood cells showed 70 per cent of the polymorphonuclear forms. Dr. Lashman informed me that the patient made an uneventful recovery.

On October 3, 1924, a white man, aged forty-four years, was admitted to my wards in the Philadelphia General Hospital. One week previously he had been drenched in the rain. He had sudden headache, went to bed and felt stiff all over. The next day he vomited and his nose began to bleed, and this continued for two days. The pain in the muscles of the lower limbs was severe, and extended from the hips to the ankles. He was told by his neighbors that he was turning yellow.

The previous history included measles, mumps and pertussis during childhood, a chancre at seventeen, a left inguinal bubo, requiring an operation at eighteen, and several attacks of gonorrhea. At the age of thirty-six he had begun the use of morphin, and had twice been in institutions for the cure of this habit, both times unavailingly. He had always used alcohol to excess, when possible to obtain it. In 1923 he was cut under the eye in an automobile accident. He lived in the cheapest lodging houses.

The findings of the physical examination were: Cyanosis of the lips, ears and fingers, yellow and injected skin and sclera, normal throat, heart and lungs, a liver that could be palpated 3 cm. below the costal margin. The urine contained a trace of albumin, hyalin and granular casts, a few red blood cells and bile pigment. There was slight anemia, no leukocytosis, normal blood chemistry. Hemolysis of erythrocytes began at 0.46 per cent and was complete at 0.26 per cent sodium chlorid solution. The van den Bergh test was positive for obstructive jaundice. An attempt to obtain the duodenal contents was unsuccessful.

On October 4, about the eighth day of the disease, and the second day of his stay in the hospital, some urine, obtained as aseptically as possible without catheterization, was injected into a guinea pig, and fifteen days later a report was received from the laboratory that the leptospira icterohæmorrhagica had been isolated from the urine of the guinea pig and the diagnosis of Weil's disease confirmed.

The subsequent course was one of rapid improvement, and on October 10 he was discharged at his own request.

Discussion. In 1886 Weil reported 4 cases of a peculiar disease, 2 of which had been observed in 1870 and 2 in 1882. The patients were all men, 3 of whom were twenty-two years and 1 twenty-three years of age. The symptoms in all cases were similar and consisted of fever, prostration, headache, dizziness, anorexia, severe pains throughout the body, especially the limbs, vomiting after the administration of calomel, diarrhea and jaundice. The spleen and liver became enlarged during the course of the disease; the urine contained albumin and casts. The fever lasted for six, nine, nine and twelve days, and in 3 of the cases a mild relapse or recurrence was observed. All the patients recovered. He discussed various diagnoses, particularly acute yellow atrophy of the liver, relapsing fever, yellow fever, bilious typhoid, a condition that had been described by Griessinger, and renal typhoid. Although he admitted that it had close affinities to abortive typhoid with jaundice and nephritis, he concluded that it was probably a *morbus sui generis*, but he did not suggest any name for it.

Subsequently many cases were reported which added three facts to Weil's description; that the disease was epidemic, that many of the patients were butchers, and that the muscles were tender, especially the calf muscles.

A febrile disease, with jaundice and often occurring in epidemics was not new. Indeed it had been described in the eighteenth century, and as early as 1812 in the United States, and many times in European medical journals. (Noguchi,[18, 19] Blumer,[2] Heiser,[7] Valassopuolo[20]). Weil, however, focussed attention upon it and described more accurately its symptoms and course.

In 1914 five Japanese investigators (Inada *et al.*[11]) stated that earlier in the year they had discovered in the blood and urine of patients suffering from the disease Odan-eke, a name that means icteric pestilence, a spirochetal organism. To this organism they gave the name Spirochæta icterohæmorrhagica and proposed the name spirochetosis icterohemorrhagica for the disease. This spirochæta is intensely pathogenic for guinea pigs and has been transmitted from one to another with persisting virulence 51 times. In the tissues of the guinea pigs it is found most abundantly in the liver, and an emulsion of the liver, if injected into susceptible animals, produces a fatal disease characterized by jaundice. The organism is pleomorphous: it is only visible by the dark-field illumination, and it stains by the Levaditi and other methods employed for spirochæta: it passes through the Berkefeld filter and grows on the Noguchi media. It penetrates the intestinal mucosa, and what is more remarkable, can penetrate the shaven abdominal skin of a guinea pig in five minutes or less. I suspect that it is possible for it to penetrate also human skin. It is found in the blood of the

human patient until the seventh day, and subsequently escapes by the urine, in which it can be found until the fortieth day, and exceptionally even longer. The blood of the convalescent patients possesses bactericidal properties, and numerous experiments were performed to discover an immune serum. The immune bodies appear from the fourteenth to the twenty-eighth day of the disease and persist at least as long as five and a half years. An immunized goat produced a serum with curative and protective properties. Arsphenamin was of doubtful use.

Another group of Japanese investigators (Ido *et al.*[9, 10]) were able to produce active immunity in guinea pigs, which is the most susceptible animal hitherto discovered, and none of which normally survive inoculation. They used livers from inoculated guinea pigs emulsified in 0.5 per cent carbolic acid and kept in an ice box for a week. This so attenuated the virus that it was possible to inoculate guinea pigs with it, and these would survive, and could subsequently be inoculated with fresh liver containing active Spirochæta icterohæmorrhagicæ without fatal results. Horse serum, obtained from horses inoculated with the organism, protected guinea pigs, and, injected into men, caused immune bodies to appear in their blood, but guinea pigs into which it had been injected did not develop immune bodies until they had received and had survived injections of living Spirochæta icterohæmorrhagicæ, a fact which may bear some relation to the greater susceptibility of the guinea pig. This horse serum was also apparently useful in curing cases of Weil's disease among human beings.

Still another series of studies by the Japanese (Inada *et al.*[12, 13]) determined that serum from immune goats inhibited the disease in all cases if injected before the appearance of jaundice. Thirty-five cases of Weil's disease were treated with serum. Seven deaths occurred, but 1 of these was moribund when admitted, and 2 died of accidental complications, so that the actual mortality was 12.5 per cent; the usual mortality in Japan being 30.6 per cent. It was found that the serum decreased the infectivity of blood drawn on the fourth day of the disease, and absolutely destroyed all the Spirochæta icterohæmorrhagicæ in the circulation. It was necessary to inject fairly large doses, 60 cc in twenty-four hours. The course of the disease is said not to have been affected, which I assume means that the duration of the fever was not shortened. They found that arsphenamin was useless (Futaki *et al.*).

In 1915, one year after its discovery in Japan, but before this discovery was known in Europe, Hüebener and Reiter[8] discovered an organism with cilia in the blood of a patient suffering from Weil's disease. It was 5 microns in length and resembled a trypanosome. This organism was pathogenic for guinea pigs, and mildly pathogenic for apes and rabbits. In a later paper they suggested the name Spirochæta nodosa. Doubtless had they had more material than

one human case, they would have studied the organism completely; as it was, they merely comfirmed the Japanese workers. They claim, however, that in guinea pigs, arsphenamin, although it does not prevent, at least delays, death.

In 1917 Noguchi,[18] having obtained living organisms from Japan, Belgium and the American wild rat, made a careful study of all. He found that it differed from other spirochæta in having more twists, in being actively motile for three months in firm agar media, and in resisting 10 per cent saponin solutions. Therefore it should be considered a new species and he suggested the name Leptospira icterohæmorrhagica, and this has been generally adopted. He found also that the leptospiræ from the three sources were probably identical for they conferred cross immunity. Inoculated guinea pigs died in from nine to twelve days and they had jaundice, choluria and extensive visceral hemorrhages. The leptospiræ were found in the organs, rarely in the blood, and in varying numbers in the urine. Apparently nothing of importance has been added since this paper.

Weil's disease, then, is a specific infectious condition caused by the Leptospira icterohæmorrhagica. This organism is found in the wild rat in many, and probably in all parts of the world. In Japan it is found in 39.5 per cent of the house and ditch rats, in America, Jobling and Eggstein[15] found it in 10 per cent of the wild rats of Nashville, Tennessee; and Noguchi[19] found it in the rats of Guayaquil and New York. Host and parasite apparently live in perfect amity, for there is no reason to assume, from the reports of the investigators, that the rats are in any way disturbed by the leptospira. The parasites escape by the urine and infect the soil, particularly if it is wet, and the disease may also be communicated by rat-bite, at least two guinea pigs bitten by infected rats developed the disease. The disease is more common in individuals working in places infected by rats, thus in Europe and America it occurs especially among butchers, in Japan among cooks and miners.

The symptomatology, as described by various observers, although essentially the same, nevertheless varies in some particulars. Valassopuolo[20] recognizes four stages: (1) Spontaneous pains in the muscles, dysphagia, erythema, and injection of the conjunctivæ. (2) Icterus (this he states, in agreement with Dawson, may be absent), oliguria, and in the urine albumin, casts and blood are found, and rising fever. The erythema stops when the jaundice appears. (3) The urinary crisis occurring about the seventh or ninth day, the amount of urine rising to 2 liters per day and even more exceptionally to 8. During this time the fever diminishes. (4) The stage of convalescence. The fever is usually remittent, there may be hemorrhage from the nose, gums and into the skin.

Dawson *et al.*[3] speak of the initial chill, the pain behind the eyes, the high fever, 103° to 105°, and vomiting in the early stage. He mentions the enlarged liver and palpable lymph glands; the rare

enlargement of the spleen. Jaundice occurred usually on the fourth day. Hemorrhages occurred in 14 of 18 cases, herpes labialis in 40 per cent of the cases. There is leukocytosis. The pulse is slow. Rare complications are retention of the urine in 3 cases and auricular fibrillation in 1 case.

Gwyn[6] mentions that the onset may be acute or gradual. Chills occurred in only 7 of 13 cases. All cases had prostration, headache, nausea and vomiting, and nearly all had abdominal pains. He lays great stress upon the muscle pains, which he regards as possibly due to myositis, caused by infection of the muscles by the parasites and this should be investigated, for it is an interesting suggestion. The muscles may be swollen as well as tender. He further suggests that myositis without jaundice may be caused by leptospira.

In addition to the jaundice he notes a scarlet flush, herpes labialis, a few rare eruptions, and lays emphasis upon the injection of the conjunctivæ. Delirium, coma and convulsions were noted in a few patients. Hemorrhages were common but purpura rare. The liver and spleen were seldom palpable. The urine contained albumin and casts. There was mild leukocytosis. The pulse rate was usually slow.

These three papers are especially quoted because all are based upon personal contact with the disease.

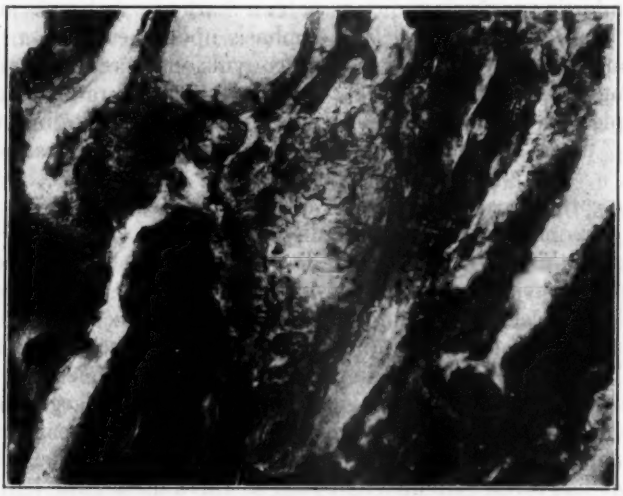
Basile[1] thinks that the jaundice is hemolytic, Heiser[7] believes that it is obstructive and caused by a plug of mucus in the common bile duct direct. The van den Bergh test in my second test agreed with this opinion. Jones and Minot[14] also indirectly support this view because they find that in the early stage, the duodenal contents contain very little bile and in the latter stage a large amount. Dawson *et al.*[3] state that the leptospira may cause the disease without producing jaundice. The diagnosis should not be difficult. If a patient has fever, jaundice and pain in the muscles, the leptospira should be sought, and if it is not found in the blood, by proper methods it can, if present, be found in the urine.

The treatment is important only in severe cases, and in these the curative serum alone offers any effective remedy. Arsenic and mercury have been suggested, but there is no evidence of their worth.

Prophylaxis is effective. Disinfecting the ground and draining the surface water checked two epidemics in Japan. Any attempt to exterminate rats in this country for the purpose of preventing the occurrence of the disease would be unjustifible, because it does not constitute any serious menace; but rats carry at least one other spirochæta capable of infecting human beings, Spirochæta morsus muris, causing rat-bite fever, and also the bacillus of bubonic plague; and the economic loss that they cause is tremendous. Therefore leptospirosis may be regarded as an additional reason for a nation wide effort to exterminate them. It would be interesting

to know if mice also carry leptospira, but I have found no information upon this point.

The disease is probably not uncommon. Many cases of catarrhal jaundice may be mild forms of Weil's disease and it is possible that myositis without jaundice and with intestinal manifestations and muscular pains also may be due to the leptospira, for Dawson's observations cannot be questioned and are supported by Valassopuolo. When suspected, confirmation should be easily obtained. The easiest method, if a well-equipped laboratory is available, is the examination of the blood by dark-field illumination. This, as my first case showed, may be positive as late as the tenth day, but should be done as early as possible. Guinea pigs are available



Photomicrograph of a section of the kidney of a guinea pig infected by the leptospira icterohemorrhagica, showing stained leptospira just above the center of the picture.

nearly everywhere in America. In the early stage they may be inoculated with the patient's blood, later with the sediment of the centrifuged urine, collected under conditions as aseptic as possible. The leptospirosis of guinea pigs is characteristic. An emulsion of the livers of a guinea pig dying of, or killed during, the disease will infect other guinea pigs and the leptospira can be maintained indefinitely.

Blumer[2] does not believe leptospirosis is common in the United States though he does not deny that it may occur. In a very careful study of the history of the type of infectious jaundice found here he notes that 72 per cent of the epidemics occur in the fall and winter, that the disease is mild, common in young persons and that the

leptospira is never found. As in his own cases a careful search was made for it by modern methods, this statement is of importance; but it is so at variance with the work in Japan and elsewhere, that, in view of its negative character, it must be accepted, if at all, with great caution. Wadsworth,[21] however, contributes some supporting evidence. In 300 cases of infectious jaundice studied by his laboratory workers, no leptospiræ were found. The conditions were unfavorable, but one of the laboratory workers, inoculating rabbits with virulent leptospiræ obtained from rats, pricked her finger, had a typical attack of Weil's disease, and Leptospiræ icterohæmorrhagicæ were found in the blood. There may be other forms of infectious jaundice but none has been hitherto definitely isolated.

Leptospirosis icterohæmorrhagia has been found in four continents, Europe, Asia, Africa and North America, from Scandinavia (Lapidus and Flaum[16]) to the tropics, for the rat is universal and the leptospira seems to accompany it everywhere.

BACTERIOLOGICAL NOTE. *Detailed Report of Study of Urine of Patient P. C.* A sample of about 100 cc of turbid and deeply bile-stained urine was received on October 6, 1924, directly after being voided. The sample was assigned to Mr. Ralph E. Otten, with directions that it be examined for Leptospira icterohæmorrhagicæ.

A 50-cc portion was centrifugalized, and the sediment examined by darkfield and by special staining method for spirochetes. Neither of these methods revealed leptospira. The bulk of the sediment was inoculated subcutaneously into a guinea pig. On the eighth day following the injection the animal showed marked jaundice, and appeared weak and inactive. On the morning of the ninth day (October 15) the animal was found dead.

A sample of urine of the guinea pig collected on October 14, showed numerous leptospiræ, demonstrated by staining methods.

Necropsy. Guinea pig, October 15, 1924. The skin, sclera, and mucous membranes of the mouth are deeply bile stained. The subcutaneous tissue, and the deeper tissues and organs show the same deep jaundice throughout. The liver is enlarged and very friable. The spleen is congested and slightly enlarged. The kidneys are congested and grossly show the signs of cloudy swelling. No hemorrhages appear anywhere.

Smears were made from the blood, liver, kidneys and spleen and stained for leptospira with negative results.

Deep tube cultures were made of the blood, liver, kidney, and spleen in 10 per cent horse serum in normal saline; in 10 per cent horse serum in beef infusion broth; in undiluted urine; and in urine diluted with 33 per cent beef infusion broth. In none of these were leptospiræ demonstrated.

Histological sections of the kidney, liver and spleen stained by

the Levaditi method showed small number of the leptospira in the kidney only. (Photomicrograph.)

Comment. The patient (P. C.) presents an interesting case from the standpoint of diagnosis for several reasons: (1) Because of its sporadic occurrence in a city where proven instances of this infection had not been recorded, thereby demonstrating the importance of bearing in mind the possibility of leptospirosis icterohemorrhagica in the study of patients presenting clinical evidences of infectious jaundice; (2) because of the fact that without animal inoculation, the patient's condition would have gone without a confirmed diagnosis. Very careful direct examinations of the urine from this patient failed to reveal the leptospira. This failure of direct demonstration of the leptospira is more to be emphasized in the examination of the blood. The chances for the direct demonstration of the leptospira in a patient's blood, even early in the course of the disease when they are the most plentiful, are not good. On the other hand, it cannot be emphasized too strongly, that confirmation of diagnosis by inoculation of guinea pigs is a very simple procedure, and at the same time a most spectacular demonstration. One might say that the sequence of events in the guinea pig infected with Leptospiræ icterohæmorrhagicæ is so definitely pathognomonic that it could scarcely be confused with other conditions, and certainly not so if cultures and microscopic examinations are made of materials secured at the necropsy of the animal.

The third point of interest is illustrated in the results of attempts to demonstrate the leptospira in the tissues of the animal. Even with an undoubted clinical course leading to death of the animal, one is ofttimes disappointed in the failure to demonstrate large numbers of leptospiræ in the tissues. As in this instance, relatively small numbers will be found on prolonged search.

Last, our failure with cultural methods when used upon material containing sufficiently large numbers of the leptospira to afford their demonstration with ease by the direct examination of smears, is of interest. Simpler methods for growing these organisms have been advanced from time to time, and from the descriptions one might be led to believe that such methods would be most useful in confirming the diagnosis in a suspected case. In experienced hands during times of epidemics direct cultures may have a place in diagnosis, but they should never be used in preference to the animal inoculation method, and should certainly never be relied upon for the diagnosis of the sporadic case.

To summarize, the laboratory diagnosis of leptospirosis icterohemorrhagica is simple It is made by the inoculation of suspected material into guinea pigs, and from the observation of the sequence of events developing thereafter in this animal. The clinical course of the disease in the guinea pig is pathognomonic, but should be confirmed by the more tedious demonstration of the leptospira in the liver, kidney or spleen of the animal.

Blood from the patient should be used during the first four or five days of the jaundice, and injected intraperitoneally in 10 cc amounts into guinea pigs. Afterward, up to the tenth day of the jaundice, both blood and urine should be used for the inoculations. Thereafter one must rely on the presence of the leptospira in the urine only. From 50 to 100 cc of urine should be centrifuged at high speed and the sediment from this injected subcutaneously into guinea pigs.

Summary. Two cases of infectious jaundice are reported in each of which the Leptospira icterohæmorrhagica was found. It is believed that they are the first cases occurring spontaneously to be recognized in Philadelphia and its environs.

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A TINTOMETER FOR THE ANALYSIS OF THE COLOR OF THE SKIN.

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A pressing need in clinical medicine is a method for measuring and recording the color of the skin. There is perhaps no other type of clinical examination subject to greater error, due in part to the

inability of the physician to describe colors, to the personal equation element in matching colors and to the kaleidoscopic changes in combinations of color exhibited in the skin of human beings.

In reviewing case reports with regard to descriptions of the color of the skin one is struck by the diversity of comparisons. Expressions, such as rose-red, slate-blue, *café au lait*, lemon-yellow, lack clinical accuracy and rank with some of our descriptive terms of size, such as large as a baby's head, an orange or a plum. In attempting clinically to portray the depth of jaundice the need of quantitative and descriptive terms is keenly and constantly felt. There are four main groups of cases in which determinations of skin color are of decided value: (1) In jaundice;[1] (2) in cyanosis;[1] (3) in conditions in which capillary dilatation and increased cell volume play a part, as in polycythemia vera; (4) in various types of pigmentation, as in Addison's disease and hemochromatosis. Furthermore, clinical application of color determination may be helpful in cases of anemia and in cases in which edema is associated.

Determination of the color of the skin is not only important from the standpoint of diagnosis, but it is valuable in following the normal fluctuations of color and those incident to treatment, particularly in the treatment of Addison's disease in which, under the Muirhead regimen, marked variations in the pigmentation of the skin are noted from time to time. This is also true in cases of jaundice, cyanosis and polycythemia.

Possible Approach to the Problem. Two possible lines of approach present themselves in the development of a skin tintometer: A comparison with color plaques, and a spectrophotometric analysis of the color of the skin. The former method consists in reproducing colors of selected areas of skin under controlled conditions by an artist employing water colors. The range of colors is determined separately for each different pathologic group. These are assembled and grouped according to their progressive increase in color. Ten plaques are employed for each scale. Intermediate color plaques may sometimes be determined with a fair degree of accuracy and interpolated by an artist trained in color work. We have been interested in this problem for the last four years, and several such tintometer scales have been developed for use in the study of selected areas of skin and the results recorded in terms of plaques Nos. 1 to 10.

There are several objections to this method: (1) The individual difficulty in matching pigment and skin; (2) the difficulty of recording the values quantitatively; (3) the tendency toward fading and impairment of the color plaques, so that it is difficult to maintain a standard scale. It is evident that the value of such tintometers is limited unless the colors involved are accurately analyzed. Per-

[1] Flagg, P. J.: An Oxyhemoglobinometer for the Clinical Measurement of Cyanosis, Proc. Soc. Exper. Biol. and Med., 1922–1923, **20**, 1.

manent value demands that these colors shall be expressed in enduring terms qualitatively and quantitatively. This difficulty is largely overcome by the use of the Munsell system of color analysis.

The second method, that of employing spectrophotometric analysis, may be applicable, but considerable developmental work is necessary to make it clinically adaptable.[2]

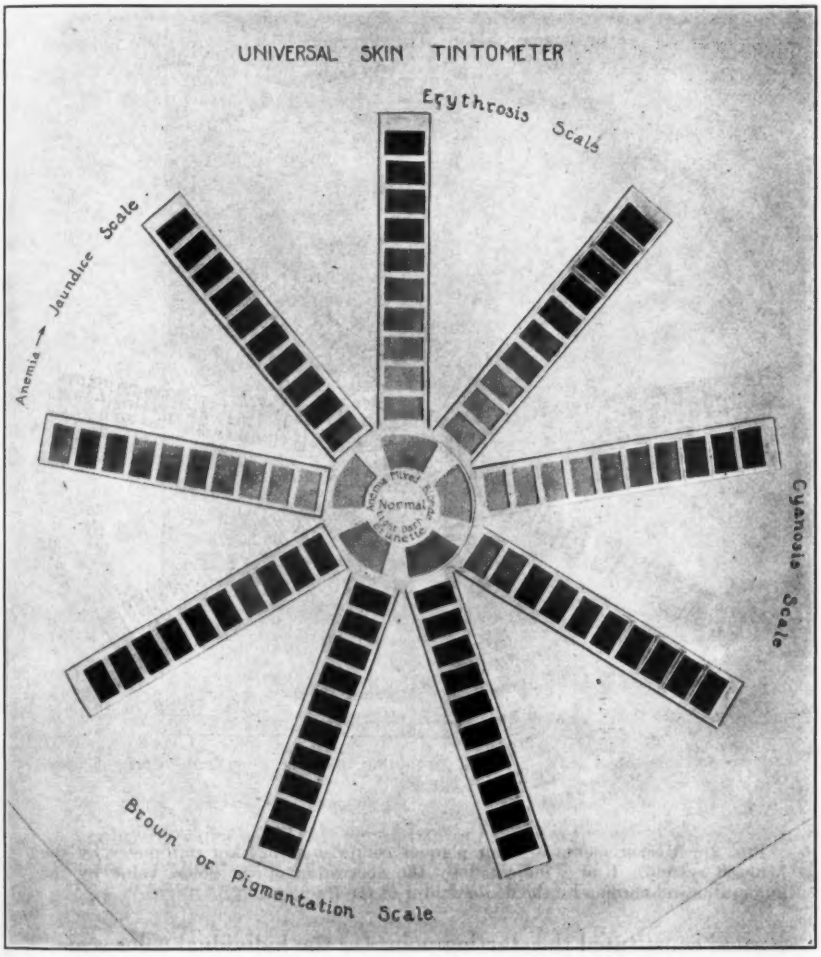

FIG. 1.—Skin tintometer composed of nine separate color scales.

The Method of Developing a Clinical Tintometer. Color reproductions were made under conditions controlled with regard to illu-

[2] Sheard of the Section on Physics of the Mayo Clinic is attempting at present to develop an instrument of this type.

mination, room temperature, posture, and so forth. The skin areas selected were the back of the hand, over the mastoid process, and the subclavicular zone.

In order to determine normal variations of the skin three groups of normal persons were selected, marked blondes, marked brunettes, and intermediate types. From these, color patches were made which indicated the maximal normal variations. The extremes of

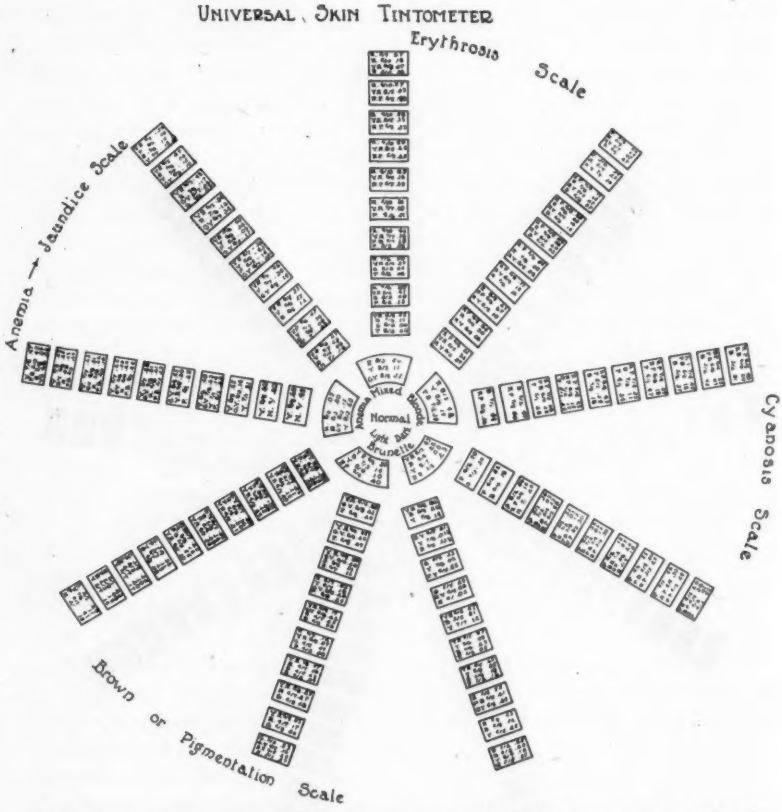

Fig. 2.—Measurements of color plaques comprising the skin tintometer by the Munsell system. Hue is indicated by the aberration of the color, value by the numerator and chroma by the denominator of the fraction.

normal constituted the starting point for the individual color scales. In developing the range of abnormal color and in constructing the tintometer, 10 cases of Addison's disease, 20 cases of polycythemia, 15 cases of jaundice and 10 each of cyanosis, anemia and edema, comprising in all about 100 color studies, were utilized.

Nine individual scales, each composed of ten plaques, were made and assembled in the form of spokes radiating from the central plaques representing the extremes of normal (Fig. 1). It was

found that at least ten colors were desirable for the different color variations observed in certain diseases. Thus there are tintometers for anemia, cyanosis, erythrosis, jaundice and brown pigmentation, each requiring ten to twenty color plaques. In order to determine the accuracy of gradations, and to assign them their correct values,

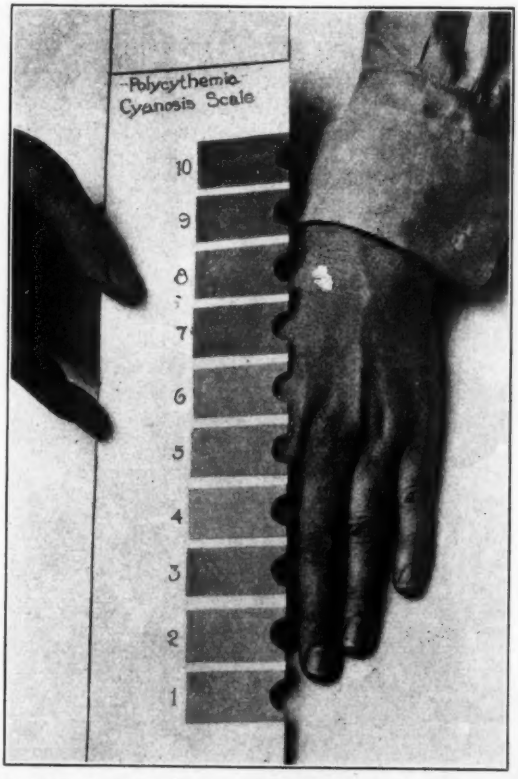

FIG. 3.—Individual color scales as employed in the routine measurements of skin color.

the color plaques were subjected to analysis by the Munsell method of color measurement[3] (Fig. 2).

The routine method in our clinical work has been comparison of

[3] The Munsell system of color measurement employs a series of color disks with perforations and slits allowing disks to be superimposed exposing various segments. Color is measured according to hue, value and chroma. The color measurements according to hue, value and chroma are printed on the back of each disk. A small motor is employed with a cardboard disk of neutral gray. The circumference of the disk is divided into degrees. Disks of selected colors are placed on motor shaft and spun. Changes in disks and in the amount of exposure are carried out until accurate matching is obtained (Fig. 4). Complete instructions are supplied by the Munsell Color Company, 461 Eighth Avenue, New York City.

the skin with separate color scales or tintometer (Fig. 3). The readings have been recorded in terms of the number of the plaque.

These plaques have all been subjected to color analyses according to hue, value and chroma (Fig. 4). In many instances color

FIG. 4.—Reproduction of the Munsell color disk index. Each color card has its measurements according to hue, value and chroma. These are placed on the disk on motor shaft and spun.

measurements were made by direct comparison of the spinning Munsell disks with the skin, and the formula recorded for future reference. Subsequently, color patches were made at will by reassembling the color disks according to the formula. Repeated comparisons indicate the degrees of color change.

The Range of Error of the Method. Studies under controlled conditions as to light, posture and temperature involving reproductions of skin color by various members of the art staff have shown maximal differences approximating 15 per cent. Similar controls involving direct comparisons of the skin with spinning Munsell disks, made both by trained and untrained observers, have shown a range of error of about 20 per cent. From this it would appear that matching of the color of the skin is difficult but that these methods, although subject to considerable error, are still infinitely better than the usual clinical description.

In determining and ascertaining the color of the skin it is the gross effect rather than the detailed color which one considers. Exact comparison of flat colors with the multiple hues seen in the detailed color of the skin is impossible. This difficulty is probably greater in the study of normal skin than it is in skin markedly pigmented. The normal skin colors are a complex mixture, comprising yellow, green, blue and red, as shown in the Munsell analysis. The skin capillaries and venules contribute the red and blue factors, while the skin itself is a mixture of green and yellow. Temperature exerts a very definite effect on color as well as the position of the part in relation to heart level. The color values vary markedly in different areas of skin in the same individual. Psychic and nervous factors at times also play a striking part.

Summary. From a large number of plaques representing artists' reproductions of skin color from approximately 100 normal and pathologic subjects a tintometer has been constructed which apparently covers adequately the entire range of color variations encountered in human skin in health and disease. The tintometer consists of multiple color scales, each composed of ten plaques, representing progressive increase in color, each plaque of which has been analyzed qualitatively and quantitatively and expressed in three dimensions of hue, value and chroma. The normal range of variations has been first determined. A separate color scale has been constructed for jaundice, cyanosis, erythrosis and brown pigmentations, each resembling somewhat the Tallqvist scale employed in the clinical determination of hemoglobin. By means of these tintometers direct comparisons with the color of the skin are made.

While the method is subject to considerable error, it offers marked advantages over the usual clinical descriptive method. The colors can be readily and accurately duplicated and new tintometer scales constructed at will through the aid of the Munsell apparatus.

Further work is in progress directed toward simplification of the method and also toward the development of a spectrophotometer method which will permit direct reading of the skin. This preliminary report is presented in the hope of indicating the need of a clinical method for accurately defining skin color and of stimulating further interest in this type of work.

GIARDIASIS: ITS FREQUENCY, RECOGNITION, TREATMENT AND CERTAIN CLINICAL FACTORS.*

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and

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Notwithstanding many recent medical papers on this subject, Giardiasis enterica deserves more thorough clinical investigation. Considered by many a harmless intestinal parasite, recent investigation indicates that it may have a real pathogenicity.

This flagellate was discovered in 1859 by Lambl,[65] and often bears his name, although he erroneously thought it belonged to the genus cercomonas. Grassi,[38, 38a, 38b] in 1877, described the same organism under the name of Dimorphus muris, and two years later renamed it Megastoma entericum. Bütschli,[15a] in 1886, again changed its name to Megastoma intestinalis, which Stiles,[106] in 1902, changed to Lamblia duodenalis. Kofoid,[57] in 1915, first proposed the name Giardia lamblia stiles, which he again changed to Giardia enterica (1920), since it was found to correspond to a flagellate originally described in tadpoles and so classified by Künstler[62] in 1882. Excellent résumés, together with biologic investigation of this many-named intestinal parasite, can be found in papers by Charles E. Simon[100, 101] and by Hegner.[42]

Hemmeter[44] observed and put on record (May, 1902) the first American case infected with this parasite and our interest in this subject dates from his report before the American Gastroenterological Association in May, 1920. Immediately after this meeting one of us (B. B. V. L.) found a duodenal aspirate swarming with the vegetative form of this parasite. Since then among 798 patients examined intraduodenally we have seen 31 cases, 20 of whom were studied and 15 were treated. In all of the cases the Giardiæ were first recognized in the living state during the duodenobiliary drainage. The morphology of this parasite is well described by Simon[100] and others. Their appearance and behavior (under high-power lens) in duodenal aspirates has been described by one of us.[74]

The purpose of this paper is to direct attention chiefly to three points: (1) The relatively increased frequency of this infection in temperate zones; (2) its clinical association with gall-tract disease; (3) its unusual stubbornness to all forms of treatment.

Occurrence in Temperate Climates. Until recently Giardiasis enterica has generally been considered a parasitic infestation of

* Read before the American Gastroenterological Association, May 25, 1925.

only tropical or subtropical zones. More recent work indicates its greatly increased recognition in temperate climates. In reviewing current literature since 1912 we find records of 3200 cases in which either the vegetative flagellates or their cysts were recognized. Chart I records the various cases reviewed. Of this total number, 1500 were reported by Musgrave[85] from his Philippine records and might justifiably be excluded from the temperate zone group. Kofoid and others[56] found 900 cases among 15,000 apparently healthy American soldiers. The third largest series was reported by Fanthem and Porter,[35] who found 187 cases among 1300 patients with diarrhea. Chart I shows that by far the largest recognition of this parasite has occurred by finding the encysted forms in stools examined with Donaldson's eosin and iodin stain.

CHART I.—TOTAL NUMBER OF CASES REVIEWED (ARRANGED ACCORDING TO NUMBER OF CASES).

	No. of cases of giardiasis.	Recognized by duodenal aspirates.	Recognized by cysts in stools.
Musgrave, San Francisco, 1922	1500	..	1500
Kofoid, *et al.*, California, 1919	900	..	900
Fanthem and Porter, Great Britain, 1916	187	..	187
Willis, Australia, 1923	84	..	84
Matthews and Smith, Liverpool, 1921	77	..	77
Castex and Greenway, Buenos Aires, 1925	70	4	66
Logan and Sanford, Mayo Clinic, 1917	66	..	66
Cheney, California, 1922	34	..	34
Le Noir and Deschien, Paris, 1924	30	..	30
Reed and Wycoff, California, 1922 and 1924	22	..	22
Woodcock and Penfold, England, 1918	22	..	22
Maxcy, Baltimore, 1921	17	..	17
Hemmeter, Baltimore, 1920	12	..	12
Kennedy and Rosewarne, England, 1916	12	..	12
Simon, S. H., New Orleans, 1922	10	3	7
Kingston, Louisiana, 1922	10	10	
Hollander, New York City, 1923	9	9	
Dionnet, France, 1923	9	..	9
McGill, Montana, 1922	9	..	9
Levin, New Orleans, 1918	6	..	6
Tsuchiya, Battle Creek, Mich.	6	..	6
Smithies, Chicago, 1918	5	..	5
Jeffrey, Michigan, 1925	5	1	4
Simon, C. E., Baltimore, 1922	5	..	5
Lyon, Indiana, 1919	2	..	2
Rodenwaldt, Poland, 1912	2	..	2
Lucas, Kentucky, 1922	2	..	2
Silverman, New Orleans, 1922	2	2	
Raue, Germany, 1923	1	..	1
Kantor, New York, 1923	1	1	
Additional unpublished cases of giardiasis (Lyon and Swalm)	20	20	
By personal communication with Philadelphia group of doctors	63	41	22
	3200	91	3089

Since the inception and wider application of duodenobiliary drainage as a diagnostic procedure, the incidence of recovery of

the living vegetative forms has greatly increased. Since 1922 a total of 91 cases has been reported in the literature in which the Giardiæ have been recovered from the duodenal aspirates. In 1923 one of us (B. B. V. L.) mentioned 11 such instances in patients, only 1 of whom had ever been in tropical or subtropical climates. In order to ascertain the frequency of this infection among residents of Pennsylvania and neighboring states, a questionnaire was addressed to Philadelphia doctors, who make routine use of the duodenal tube. The replies indicate a surprisingly increased recognition of this parasite in duodenal aspirates, as follows: M. E. Rehfuss, 12; H. L. Bockus, 12; M. M. Rothman, 10; H. J. Bartle, 3; H. M. Eberhard, 2; J. Q. Thomas and S. Immerman, 1 each; a total of 41 cases. Furthermore, through the courtesy of Drs. Noone, Usher and Waltz, we have learned that they have observed 14 cases at the Children's Hospital in Philadelphia within the last four months in children between two and six years of age. During 1924 8 additional cases were recognized, all occurring in the last quarter of the year. They attribute the increased incidence of recognition to a more careful search for this parasite, recently inaugurated in routine stool work. No duodenal intubations were done. In the majority of their cases the diagnosis was also made accidentally, some of the cases coming through out-patient services and others admitted to the wards with pneumonia, or other acute infections which masked any definite clinical symptoms of Giardiasis. Among their group of children, diarrhea, while conspicuous, occurred in only 7 cases. Other symptoms consisted of nausea, vomiting, restlessness and insomnia. One had convulsions. This series of cases, together with our own, reaches a total of 83 cases observed in Philadelphia by a small group of doctors. The incidence is no doubt much larger, many cases not being reported and many more escaping recognition. Obviously, this infection in temperate climates is of some importance.

Method of Dissemination of Giardiasis. There is much evidence that Giardiasis is transmitted chiefly by the cysts, which are very resistant and may be eliminated for years by individuals who are symptom-free and apparently cured. Grassi successfully inoculated himself by ingesting the cysts. As in typhoid, so in giardiasis, fingers, food and flies are the chief offenders. Galli Valerio and Stiles have both shown that the house fly may carry and deposit the cysts. This may account for the small epidemic in the Children's Hospital mentioned above, which occurred in the fall and winter months.

Various rodents have been suspected of spreading the infection, but Simon, who has extensively studied this question,[100] believes that human infestation is of human origin, and he seems to have established specific differences existing between human Giardiæ and those of the house and meadow mouse. Culture rats and wild

rats cannot be infected. He believes that there is no basis for the assumption that human infection is referable to rats and mice. So too, Hegner[43] believes that the rabbit and cat are parasitized by a species distinct from that living in man.

Musgrave[85] points out that air-borne dust containing cysts, settling on vegetables, cereals, fruits and other foods exposed to the air, may serve as a means of dissemination. This also may apply to small water courses, shallow wells or contaminated springs, as mentioned by Smithies.[104]

The likehood of such methods of transmission is suggested by the fact that in children particularly, several members of the family, may become simultaneously infected. It is possible that by air-borne routes the respiratory tract may be invaded, for Giardia cysts have been found in bronchiectatic secretions. In 3 cases observed by Bartle (personal communication) all had chronic bronchitis. The great increase in this infection noted during the World War among returning troops lends color to the belief that direct contact with dejecta and generally unhygienic living conditions tend to spread the disease.

Pathogenicity. Can such intestinal parasites be responsible in part for many obscure gastrointestinal disorders? The concensus of more recent opinion is in favor of this point of view, and our experience reported herewith, is in accord.

From a review of our cases we believe that Giardiæ may constitute a contributing factor to a state of disease or dysfunction particularly involving the gall tract, the duodenum and jejunum. Very little seems to be known as to why this parasite apparently elects its chief localization in the duodenum and jejunum. By its peculiar sucker-like peristome it attaches itself to the duodenal epithelium and even penetrates within the deeper glandular layers, and so distorts the duodenal cells as to be readily recognizable by microscopic examination of fresh aspirates. This injury to the duodenal mucous membrane has also been noted at autopsy by Galli Valerio.[111]

It is our opinion that such constant irritation of the duodenum seems capable of producing a catarrh, and possibly an inflammatory edema, and if excessive in the neighborhood of the ampulla might produce a mechanical obstruction of bile, with a catarrhal form of jaundice. Indeed, it is conceivable that the bodies of the Giardiæ swarming in the duodenum in uncounted millions may of themselves produce such mechanical obstruction of the common duct. It is considered by some[102] that the Giardiæ, with the whip-like movement of their flagella, may favor the introduction of bacteria into the common ducts, and initiate an ascending infection. Microscopy of duodenal aspirates definitely indicates that a pronounced duodenitis exists in many cases. This may be an associated factor in the production of duodenal ulcer, as observed in 1

of our cases. It has been found that their presence interferes with the proper elaboration of the succus entericus of the duodenum and jejunum. Whether this is cause or effect cannot be definitely stated, either from the evidence we have reviewed or from our personal observation.

We have been particularly interested in the clinical association of Giardiasis and gall-tract disease. Among our 20 cases, 18 of them had disease of the biliary tract, 14 of them had infected bile, 12 had definite catarrh and exfoliation and 7 suggested gall stones, proved by operation. Four were jaundiced and 6 showed evidence of diminished pancreatic function, 1 patient having a tumor of the pancreatic head. That this is not an uncommon experience is indicated by a review of recent literature in which the association with gall-tract disease is mentioned by Smithies, Knighton, Silverman and Kantor, and by personal communication from Rehfuss, Bockus, Eberhard, Rothman and Bartle. However, the frequency of association with gall-tract disease cannot be very great, since we have been able to demonstrate Giardiasis in only 20 out of 798 patients in whom duodenal aspirates were carefully studied, and in whom various types of gall-tract disease was recognizable in approximately 80 per cent.

Do the Giardiæ Invade the Gall Bladder or Bile Ducts? In connection with its relation to gall-tract disease, a most interesting point, as yet unproved, is whether the Giardiæ themselves do actually invade the gall bladder. We have not been able to trace any single authenticated instance. Throughout the literature this finding has been attributed to Smithies on account of his verbal discussion of Hemmeter's paper in 1920.[44] Reviewing Smithies' own contribution[104] to which he referred in that discussion, we find it concerned a study of 1000 patients among whom were found 93 cases of protozoal infection, 5 of which were Giardia. Although Smithies states "Our studies of specimens in gall bladders and appendices removed at laparotomy indicates that in these parts of the gut cysts of protozoa may lurk for years," yet there is *no specific statement* in that paper that Giardiæ themselves were found in any gall bladder. It has been taken for granted through the ensuing literature that this is a fact.

In 2 reported cases in which the gall bladder was diligently searched for Giardia, they were not found. Silverman[102] states: "We found the same character of bile as was recovered by the duodenal route, but while the latter contained myriads of Giardiæ, neither did the gall-bladder mucosa nor its contents reveal any of the parasites or their cysts." In a second case reported by one of us,[74] in whose duodenum numerous Giardiæ were found, at a later operation no Giardiæ were found either in gall-bladder bile or scrapings from the mucous membrane of a gall bladder containing 155 stones. However, it is interesting to note that in this particular case, three

years later, studies of stools after brisk purging failed to demonstrate either flagellate or encysted forms.

There is considerable *clinical* evidence, however, that infestation of the gall bladder or ducts is a possibility. We and others have noted patients relapsing under various forms of treatment, in whom for weeks or months Giardiæ could not be demonstrated in duodenobiliary aspirates; then they suddenly appeared, conspicuously and in several instances, exclusively in the "B" or gall-bladder fraction. This occurred in 5 of our own patients, and in several seen by Bockus (personal communication) and in 1 by Knighton.[52]

The latter assumes that his case had an infestation within the gall bladder and believes that reinfestation took place in the duodenum from this source, since he could find parasites only in the centrifuged "B" fraction after magnesium sulphate stimulation. He says: "If there is any doubt as to Lamblia intestinalis infecting the bile passages, this should settle the question."

Symptoms. Except during the acute period of infection, when there is often diarrhea (especially in children) there does not seem to be any definite symptomatic picture which can be ascribed to Giardiasis. There may be vagus or definite symptoms of the gall bladder ulcer group, as mentioned by Cheney,[24] McGill[31] and noted frequently in our cases. Cheney suspects Giardiasis in all chronic cases of an indefinite type, particularly those with added nervous symptoms, "all gone" sensation and irritable intestines. Sidney Simon,[102] in 8 cases, quite frequently found increased abdominal gas and abdominal cramp-like distress, but believes that no one symptom or group of symptoms is a reliable diagnostic sign, but a suspicion of Giardiasis should be entertained in all cases of indefinite diarrhea and increased abdominal gas. Galli Valerio[11] observed in all of his cases alternating constipation and diarrhea with general depression, pale skin and mucous membranes. Among his cases true dysentery did not occur.

Through the courtesy of Profs. M. R. Castex and D. Greenway, of the Faculty of the University of Buenos Aires, we have received the following notes from a paper shortly to be published in the *Prensa medica argentina*. In a study of 614 cases[21] these authors observed 70 instances of Giardiasis associated with other protozoal parasites. In 4 cases they demonstrated the Giardiæ during duodenobiliary drainage. It reached 11 per cent of their parasitic findings and occupied the fifth place in their parasitical studies. Among the clinical symptoms they found in some cases high-grade constipation with spontaneous evacuations every second or third day, improved only by proper diet. In other cases constipation alternated with diarrheic episodes, with abdominal colic, tenesmus and abundant mucus. In some of the constipated patients laxatives provoked acute enterocolitis with anxious state of feeling, and intensified the toxemic symptoms. Anorexia, nausea, pyrosis,

regurgitation, vomiting, gastric discomfort, abdominal distention and acute pain in the right upper abdomen occurred most frequently in their patients. Diffuse abdominal pain or pressure and more or less enlargement of the liver was found in many of them. Headache, physical and mental weakness, paresthesias, agripnias, neuralgias and general toxemic symptoms are emphasized by these authors.

Discussion of Symptoms in Our 20 Cases. (Chart II.) *State of Bowels.* With the exception of 1 patient, all of our last 20 cases, now reported, occurred among adults. There were 9 females and 11 males. Although diarrhea seems to be a symptom commonly mentioned in the literature, it is far more frequent among children. It would appear that this parasite when chronically implanted is more apt to be associated with constipation. Twelve of our cases had definite constipation, 5 very obstinately; 5 had normal bowel function and only 3 diarrhea. In 1, a boy, aged eleven years, the diarrhea appeared due to Giardia, and represented a freshly acquired infection. Of the other 2, 1 had gastric anacidity, with associated pancreatitis and the other intestinal tuberculosis, which might account equally well for the diarrhea. Therefore, in our personal experience with the adult form a state of diarrhea has been unusual. In our group of patients the Giardia was the only intestinal parasite encountered, although it has been commonly found by other observers to be associated with entameba, trichomonas, chilomastix, blastocystis hominis and other parasites. Among the American cases the majority of these mixed infections have been reported by doctors living on our southern and western coasts, where intestinal parasitic infections are more common.

Pain. Abdominal pain, occurring in 14 cases, was usually noted in the upper abdomen, more often in the right upper quadrant. It varied from a vague pain distress to definite generalized cramps in 1 case of active diarrhea. Some patients complained of an "all gone" sensation, not unlike a hunger pain.

Other Digestive Symptoms. Abdominal distention was a common finding, with belching noted in 12 cases and flatulency in 11. Nausea occurred in 6, with vomiting of a biliary type in only 1 case. Nine had intestinal stasis, as evidenced by the carmine test meal and barium progress meal.

Toxic Symptoms. Headache occurred in 11 cases; it approached in severity the biliary migraine type in 5. Dizziness was complained of by 6 of these patients, 4 to a mild extent. One patient noticed it especially on suddenly lying down, getting up or turning quickly. One patient had definite vertigo, falling on the street on several occasions. In 7 cases the clinical picture suggested hepatic intestinal toxemia, although indicanuria was present in only 5. Seven patients had ill-defined, but definitely increased, restless nervousness.

Other Symptoms. Twelve patients complained of moderate to severe weakness. Cardiac palpitation was noted in 8 patients and 3 associated with myocarditis. One patient had many fainting attacks after the evening meal, and was particularly intolerant to alcohol and tobacco. Loss of weight was conspicuous in 8 patients, ranging between 8 and 39 pounds. Enuresis or priapism was noted in 3 instances. In 3 cases there was an associated arthritis, in 2 of whom it took the hypertrophic variety with much deforming of hands and feet, and a noticeable soft periarticular swelling. The third case fell into the Paget's group. In all 3 there was a noticeable whiteness of the skin and mucous membrane, due to anemia.

Many of the above group of symptoms were very promptly relieved after instituting appropriate treatment. After reviewing the symptoms occurring in our cases, one is left with an uncomfortable feeling of uncertainty as to whether they too may not have occurred in spite of, rather than because of, the Giardiæ.

Laboratory Studies (Chart II). It has been stated that Giardiæ are intolerant to hydrochloric acid and that they might therefore more frequently occur in cases in which gastric acidity is lowered. Our experience, however, does not confirm this. In 15 of the 20 cases in whom fractional analyses were recorded, 8 showed definite hyperacidity, 3 normal acidity, 3 subacidity and only 1 anacidity.

In 19 of the 20 cases occult blood to benzidin was tested in the stomach contents, duodenal contents and stools. In 12 instances it was +1 to +2 in the stomach; in 7 patients, +1 to +2 in the stools; in 3 patients, +1 in the duodenal contents. In 2 of the latter instances there was definite duodenal ulceration. This comparatively infrequent finding in the stools is in contrast to the more frequent bleeding from the intestinal tract infected with Entameba histolytica. In no instance was there gross blood recognizable in the stool.

In no patient was there anything distinctive in urinalysis, only 5 instances of indicanuria being observed among 20 cases.

There was definitely decreased pancreatic enzyme activity in 6 patients. In this connection other observers have noted that the size of the stool is apt to be large and greasy when no diarrhea is present. This was not noted in our cases.

The blood count seems to indicate a distinct tendency to anemia and a slight leukopenia with relative lymphocytosis. In 14 cases complete blood counts were done one or more times, and in 9 of these the hemoglobin ranged between 57 and 82 per cent and averaged 68 per cent; the leukocyte counts ranged between 4600 and 8800, with an average of 6300; lymphocytes between 13 and 53 per cent, with an average of 29 per cent; the eosinophilia was noted in only 8 of the 14 cases, in no instance went above 4 per cent and averaged for the group a normal 1.3 per cent. Absence of noteworthy eosinophilia therefore seems to distinguish this infection from other forms of parasitism.

CHART II

Case. No.	Age.	Sex.	Duodenal vegetative forms.	Cysts in stools.	Constipation.	Diarrhea.	Normal bowel function.	Colitis.	Enterocolitis.	Pancreatitis.	Associated with gt. disease.	Gall Tract infection.	Gall Tract catarrh.	Gall stones.	Jaundice.	More in "B" than "D" bile.	Relapsing from "B."	Static "B" bile.	Associated with App'x. dis.	Pyloro-duod. ulcer.	Duodenitis.	Gastric acidity.	Associated with arthritis.
I	11	M.	+[4]	+	..	+	..	..	+	..	+	Sta. aur. vac.	+	..	..	..	..	+	..	..	+	Hyper.	..
II	30	M.	+[4]	+	..	..	+	..	..	..	+	B. coli; no vac.	+	..	..	..	..	..	Out	..	..	Normal	..
III	48	F.	+[4]	+	+[3]	..	..	+	..	..	+	Sta. aur.	+	..	..	..	..	+[4]	..	..	+	Hyper.	+
IV	39	M.	+[4]	..	..	..	+	..	..	..	+	+	..	..	+	+	..	+[2]	..	..	+	....	..
V	59	M.	+[4]	+	+[2]	..	..	..	..	..	?	B. coli vac.	..	..	..	+	+	+[3]	..	..	+	Sub.	+[4]
VI	50	F.	+[4]	+	..	+	..	+	..	+	+	Sta. aur., nonhem. st., oper.	+	+	..	..	..	..	+	..	..	An acid	..
VII	49	F.	+[4]	+	+[4]	..	..	+	..	+	+	Sta. aur.; B. coli vac.	+	..	..	+	+	+	..	..	+	Sub.	..
VIII	35	F.	+	+	..	+	..	+	+	..	..	Not cult.											
IX	59	F.	+	+	+[2]	..	..	..	..	..	+	Hem. st., sta. aur. vac.	+	?	+	..	..	+	..	..	..	Hyper.	..
X	68	M.	+[2]	..	+	..	..	+	..	+	+	Not cult.	..	..	+[4]	..	..	..	..	..	+	....	..
XI	33	M.	+[2]	..	+[3]	..	..	..	..	..	+	....	+	?	+	+	..	+[3]	+	+	+	Hyper.	..
XII	25	F.	+	..	+	..	+ Now	..	..	+	+	St. nonhem.	..	..	..	+	..	..	Out	..	+	Normal	..
XIII	43	F.	+	..	+	+	..	..	..	+	+	....	+	..	..	+	..	+	Out	..	+	Normal	..
XIV	20	F.	+	..	..	..	..	..	..	..	+	Sterile	+	..	..	..	..	..	..	..	..	Hyper.	..
XV	39	F.	+	..	+	..	..	..	..	..	+	Sta. aur., nonhem. st. vac.	+	..	..	+	..	+[3]	Out	..	+	Hyper.	..
XVI	40	M.	+	..	+	+	..	..	..	..	+	Sta. aur., no vac.	+	?	..	+	+	+[2]	..	..	+	Sub.	..
XVII	57	M.	+	..	..	..	+	..	..	..	+	+	+	?	..	+	+	+	Out	..	+	Hyper.	..
XVIII	21	F.	+	..	+	..	..	+	..	..	+	+ nonhem. st., Sta. aur.	+	?	..	..	..	+	..	..	+	Mod. hyper.	..
XIX	56	M.	+	..	..	..	+	..	..	..	?	....	..	..	..	..	+	+	..	..	+	....	..
XX	50	F.	+	..	+	..	..	..	..	..	+	+ B. coli	..	..	..	..	..	+[3]	..	..	+	....	+
Totals	..	..	20	9	12	3	5	6	2	5	18	14	12	..	4	9	5	14	2	2	15	8 hyper. 3 nor. 3 sub. 1 anac.	3

CHART II.

Abdominal pains, distress.	Belching.	Flatulency.	Nausea.	Headache.	Dizziness.	Increasing nerv's.	Weakness.	Palpitation or cardiac.	Enuresis-priapism.	Hepatic intest. toxemia.	Indicanuria.	Intest. stasis.	Loss of weight.	Hemoglobin, per cent.	Leukocytes, thousands.	Lymphocytes, per cent.	Eosinophilia, percent.	Duration of observation, mos.	Occult blood. Stomach.	Occult blood. Duodenum.	Occult blood. Stools.
Cramps	..	..	..	...	..	+	+	...	+	..	..	..	...	85	5.6	41	..	30 mos.	+	..	+[2]
All gone	+	+	..	+[4]; bil. migr.	..	..	+	+; fainting eve.	..	..	..	+	+	95	...	17	..	9 mos.	+		
Low abd. and gas	+	+	+	+[4]; bil. migr.	..	..	+	+	..	+	..	+	...	73	5.9 5.2 6.8 7.6	13 to 27	1 to 4	10 mos.			
Up. rt. q.	+	+	..	Bil. migr. sev.	..	..	+														
...	..	+	..	...	..	..	..	...	..	..	..	..	+	65	..	21	..	6 mos.	+		
Epigast.	+	+	..	+	..	..	+	...	..	+	+	+	+ 39 lbs., 1 yr.	82	4.7	30	1	1 mo.	+[2]	..	+
High epigast. of up. r. q.	+	+	+	+	..	..	+	+	..	+	+[2]	..	..	97 88	..	25	..	4 mos.	+	+	+
Up. r. q.; low r. q.	..	+	+	+	..	..	..	+	..	..	..	+	+ 8 lbs., 6 mos.	70	6.0	53	1	.....	+		
.....	..	..	..	+	..	..	..	...	..	..	+	..	..	57 60	4.6 5.5	13 7	1 1				
Midepi. gast. gas	+	..	..	Bil. migr.	..	..	..	...	..	..	..	+	..	68 to 78	5.7 to 7.2	33 to 43	2 to 3	15 mos.	+	+	+
Up. r. qt. attacks	+	..	..	+[3]	+	+	+	...	..	+	..	+	..	65	6.2	37	2	.....	+	..	+[2]
Up. r. qt. sore.	+	..	..	Bil. migr.	+	+	+	+ myocardial weak.	..	..	..	..	..	70	4.6	19	3	12 mos., by letter	+	..	+[2]
.....	..	..	..	...	..	..	..	.....	..	..	..	..	..	..	..	..	..	.....	+		
.....	+	+	+	...	+	+	..	Occas.	..	+	+	+	+	78	5.8	29	..	6 mos.			
Gen. abd. distress	+	+	+	...	+	+	+	+ dysp.	..	+	..	+	+ 14 lbs., 6 mos.								
+	+	+	+	..	..	..	+	..	+ freq.	..	..	..	..	..	..	..	..	10 mos.	+	+	
.....	..	..	..	...	+	+	+	.....	..	+	+	+	..	..	..	..	..	5 mos.			
.....	+	+	..	...	+	+[2]	+	...	+[2]	..	..	..	+ 9 lbs., 1 yr.	..	..	..	..	30 mos.			
.....	..	..	..	...	+	+	..	...	..	..	..	..	..	..	..	..	..	12 mos., *ca* 34 drain.			
14	12	11	6	11	6	7	12	8	3	7	5	9	8	..	..	..	..	....	12	3	7

Treatment. A review of the literature of Giardiasis brings out prominently the fact that this parasite is by comparison with many others remarkably resistant to treatment. It is highly probable that as yet no specific treatment has been developed. The following drugs in various dosage, either alone or in combination, have been tried: Tannic acid, ichthyol, hexamethylenamin, methyl blue, dilute hydrochloric acid, beta-naphthol, thymol, bismuth salicylate or subnitrate, guaiacol carbonate, turpentine, salol, quinin, sulphur, copper arsenite, Chaparro amargoso, calcined magnesia, soda bicarbonate, castor oil, calomel, santonin, emetin, ipecac and arsphenamin.

Various writers have recorded cures, particularly with thymol, hexamethylenamin and arsphenamin, but the duration of observation of many of these cases was hardly long enough to make such claims valid in view of the notable tendency of relapse. As long as any single parasite is left behind, repropagation seems possible. In 1917 Yakimoff[118] found that arsphenamin was extremely effective in white mice. This was confirmed by Kofoid,[55] in 1918, who experimented on rats. Afterward its use was applied in human beings with perhaps the largest measure of success attributed to any drug. It must be given in full doses, inasmuch as small initial doses seem merely to stun the parasite and develop in it a tolerance for the drug.

In the small epidemic of 22 cases observed at the Children's Hospital of Philadelphia treatment was attempted in approximately 30 per cent. Thymol and hexamethylenamin were without effect In 4 cases sulpharsphenamin was used intramuscularly without appreciable result. One case, three years of age, received four large doses, one injection of 2 dg. and three of 3 dg., and still continued to relapse. Temporary improvement could be secured, but relapses occurred.

One or two writers have used arsphenamin intraduodenally, and have noted improvement.

It is very important, however, in reviewing treatment of this disease, to definitely separate clinical improvement from parasitical cure. Castex and Greenway, of Buenos Aires (personal communication) state: "We tried without any result the use of thymol, calomel, turpentin, quinin, methyl blue, sulphur, arsphenamin, bismuth salicylate, beta-naphthol and guaiacol compound. We have not the same enthusiasm for arsphenamin that the American authors have, having given it intravenously in full doses with no appreciable final results. In our hands the two best remedies have proved to be the French stovarsal Poulenc and the German yatren 105 Behring." They precede treatment with the use of cholagogues or biliary extracts and by repeating or alternating this treatment, obtain excellent results and could free patients of their Giardiasis, generally in one or two months. Treatment with stovarsal Poulenc

was carried out in the following way. For three days, 3 tablets of 0.25 gm. a day, three days' rest; 3 tablets of 0.25 gm. for three days, then fifteen days' rest. If the stool still contains Giardia cysts stovarsal is repeated a second time. If no cysts were found bile extracts were given for five days and stools reëxamined. With yatren 105 Behring the treatment was carried out as follows: For ten days 3 cachets daily of 0.75 or 1 gm., then ten days' rest. Examination of the stools and according to the result, the yatren was repeated one or more times. In their hands yatren gave the best results.

Our Own Therapeutic Experience. In our own experience, because the majority of our cases were associated with gall-tract disease, we relied partly on the effect of biliary drainage with magnesium sulphate intraduodenally. This drug seems to have great power in stunning or inhibiting the movement of Giardiæ, many millions of amotile forms being subsequently washed out of the duodenum from time to time. In continued usage it may be more potent than we think for Giardiæ within the duodenum and jejunum, but has no power to attack the parasite if lodged in the biliary channels. We have noted the parasite suddenly reappearing after intervals of absence running into months, and as previously stated in 5 instances recognized only in the gall-bladder fraction bile.

The same opinion may be expressed in regard to dimol, a phenol derivative, with which we have experimented with variable results. In 1 of our 2 cases in which we believe a cure might be claimed dimol was the only drug in addition to magnesium sulphate with biliary drainage, that was used.

In Case I ten weekly drainages were given, followed each time by transduodenal lavage with 500 cc of 1 per cent dimol. Although originally present in great abundance, no Giardiæ were found after the second treatment, although rechecked on the fourteenth day, and thereafter at weekly intervals for three months. The diarrhea in this boy, aged eleven years, was promptly controlled and was therefore assumed to be due to the Giardia. There was general symptomatic improvement and a gain in weight of from 79 to 102 pounds, in thirty months. On a final recheck made twenty months after discontinuing treatment, we could find no vegetative forms in the duodenum and no cysts in the stools after brisk purging.

Our second apparent cure occurred in Case XIII. A woman, aged forty-three years, was given thirteen biliary drainages, twelve instillations of 100 cc of 2 to 4 per cent dimol, in sterile water, to a total of 8½ dr. In addition, neoarsphenamin was used intraduodenally on the fifth and tenth days, in dosage of 0.3 to 0.45 gm. The Giardia disappeared after five drainages, the fourth dimol and the first intraduodenal neoarsphenamin. The drainages were then continued for about eighteen months at monthly intervals, and at no time thereafter were Giardiæ again detected. Marked general

improvement was secured and a gain of weight from 96 to 106 pounds.

That it is unwise prematurely to credit the effectiveness of any drug in a condition as stubborn to treatment as Giardiasis, is evidenced by Case XVII, a man, aged fifty-nine years, who was given twenty-four drainages, twenty-four dimol instillations in 1 per cent solution and one intravenous neoarsphenamin of 0.6 gm. The Giardiæ disappeared after the fourth day's treatment, but a relapse occurred six months later, although marked general improvement was secured. This patient was given dimol daily by duodenal tube for twenty-one days.

In Case V, a male, aged fifty-nine years, with hypertrophic osteoarthritis, and a possibility of focal infection in the gall bladder, the patient was given *continuous* biliary drainage for seventeen days, with a daily duodenal lavage with silvol solution, 1 to 5000, sodium iodid intravenously and hexamethylenamin by mouth. The Giardiæ disappeared after the eighth day of treatment, but a relapse took place two weeks after drainage was discontinued. Five years later Giardia cysts were found in abundance in the purged stools of this patient. Moderate improvement in the arthritis was secured.

Case VI, a female, aged fifty years, with gall stones, whose duodenum contained the vegetative forms, was not treated medically. Her gall bladder and contents were removed. No giardiæ were found in the gall-bladder bile or mucosal scrapings, and yet three years later careful search of liquid stools failed to demonstrate their presence. This patient has secured complete improvement.

Case XV, a female, aged thirty-nine years, observed on the first day of acute catarrhal jaundice, was found to have a pronounced duodenitis and swarming Giardiæ. Later drainage findings indicated an intermittent catarrhal obstruction of the cystic duct. Dizziness and lack of endurance were conspicuously complained of. There was moderate anemia, leukopenia and lymphocytosis. She was given twelve drainages, followed by twelve transduodenal lavages with Ringer's solution, eight intraduodenal instillations of silvol, 1 to 5000, and four of 2 per cent dimol. The Giardiæ disappeared within three weeks and have not since been detected over a period of four months. This period of observation in Giardiasis, however, is too short to be of final value, although marked general symptomatic improvement was secured.

Case XVI, a male, aged forty-two years, with pronounced symptoms of gall-tract disease and drainage findings of cholecystodochitis and suggested lithiasis, had myriads of Giardiæ. He has been under observation for three months, and has had nine drainages,

five transduodenal lavages of silvol, 1 to 5000, and seven of dimol, 1 to 2 per cent. The Giardiæ disappeared from the duodenum and remained absent for five weeks, when they reappeared in abundance but were found only in the static gall-bladder fraction bile.

Case XVIII, a female, aged twenty-one years, was given eighteen drainages followed by 2 per cent dimol, transduodenal lavage, and in addition, given dimol tablets internally by mouth, for one month; 0.9 gm. of arsphenamin was given on the third day. The Giardiæ disappeared after the third weekly drainage, and have not been detected since then, over a period of five months, which we believe is not sufficiently long to claim a definite cure. Marked general improvement was also secured in this case.

Case XX, a male, aged fifty years, under observation for one year, has been given thirty-four drainages at weekly intervals, 1 per cent dimol by intraduodenal lavage and two intraduodenal injections of neoarsphenamin of 0.45 and 0.6 gm. The Giardiæ promptly disappeared, but after three months recurred intermittently in "B" bile, in moderate numbers, in spite of weekly drainage. Neoarsphenamin by duodenum nauseated this patient and was discontinued. An autogenous vaccine of B. coli from bile cultures was given, with improvement. Dimol tablets were taken by mouth between drainages, but the Giardiæ still persisted.

The other 6 cases were of the same general character, and treated similarly, with no definite cure of the Giardiasis, relapses occurring unexpectedly after apparent early success.

From the citation of the foregoing cases it will be evident that caution must be observed in claiming a definite cure in Giardiasis. On the whole, our experience with treatment has been distinctly disappointing.

Summary. 1. Giardiasis enterica is an intestinal parasite of clinical importance, quite frequently observed in temperate climates.

2. It seems to have a definite pathogenicity and in adult patients is most often found clinically associated with disease of the gall bladder, bile ducts and duodenum.

3. It is unusually resistant to all forms of treatment. It is highly probable that as yet no specific treatment has been developed.

4. Owing to the frequency of relapses observed, caution should be exercised in prematurely claiming an actual cure in Giardiasis.

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TROPICAL SPRUE IN A CHILD SIX YEARS OF AGE.

With Isolation of Monilia from Patient and Tissues of Inoculated Animal.

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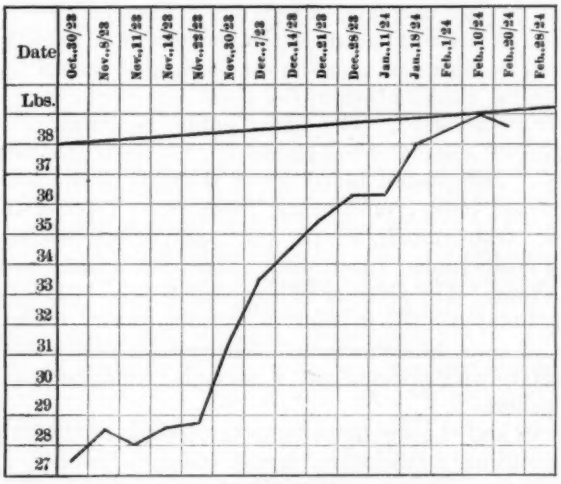
The subject of tropical sprue has been so carefully studied by Col. Bailey K. Ashford, Medical Corps, U. S. A., and has been presented by him in Oxford Medicine in such a masterly way, that there seems very little further to be said on the subject today. Nevertheless, additional confirmation of some of his hypotheses cannot come amiss. Comparatively so few cases have been seen in the U. S. A. that it would not have been strange if we had missed a diagnosis which two of the largest schools of tropical medicine in the world had failed to make. But now we have become not only a country with tropical dependencies but also a nation of travelers, and many of our citizens now engage for shorter or longer periods in business or missions abroad and are thereby exposed to these tropical infections. We therefore need to become more familiar with their manifestations.

It is with the idea of bringing more forcibly to our attention the fact that such cases may be and are found in the U. S. A., and with the hope of familiarizing ourselves with the symptoms, clinical findings and treatment, and to present proof of the existence of the Monilia psilosis in tissues of the inoculated guinea pig, as shown by the microphotograph, that this case is presented.

The patient, a little girl aged six years, came under observation October 30, 1923. The family history was negative. She was a seven months' child, and for the first few months of her life there were some feeding difficulties and a prolonged attack of whooping cough which caused some delay in growth and development. However, at eighteen months she was practically normal. Shortly before she was three years of age, she went with her parents to India

for eight months. While there she had a bad infection with both seatworms and roundworms. At the age of four years the child returned to India, where she remained until recently. She was perfectly well and unusually athletic for a child until June, 1923, when she had an acute diarrhea with fever. At first there were from six to twelve stools a day. She grew very weak, lost weight, was dull and apathetic, but as a rule had no pain.

After failure to conquer the diarrhea at home she was sent to a famous school of tropical medicine for study and observation, where roentgen-ray examination and extensive microscopical and bacteriological studies were made, with a final conclusion that the disease was due to a chronic dilatation of the large intestine (Hirschsprung's disease). She lost weight progressively while in hospital.



Weight chart.

Stools alternated between constipation and diarrhea. Failing to improve, the mother started home with the child, weighing then 25 pounds. Further studies were made of the case in London, with the opinion that the case was tuberculous, though no tubercle bacilli were found on eight examinations of the stools.

On entrance here the child presented the following picture: Marked emaciation and asthenia. She came in a wheel chair; could support her weight, but was very weak and did not walk. Her skin was pale, her muscles soft and flabby. Her height was 40.3 inches; weight 27½ pounds; pulse 114; temperature 97.4. Her pupils were regular, equal in outline, and responded normally to light; there were accumulations of strings of mucus under the lids. The tongue was coated. There were a few ulcers on the floor of the mouth and on the under surface of the tongue, and a marked

redness of the tip and sides of the tongue. There was excessive secretion of saliva. We were told that this ulceration healed and then recurred. Recently the teeth began to annoy with a feeling of soreness. The heart and lungs were normal, except as for such weakness as would be expected with the general malnutrition. The abdomen was greatly distended with gas. The patient was troubled for some time after every meal with marked hiccoughs. The upper margin of the liver was normal; the lower margin lay two fingers' breadth above the rib margin. The spleen was enlarged and crowded up by gas. There were slightly enlarged lymph glands, palpable in the groin, axilla and in the inner surface of the elbows. The knee reflexes were diminished. She suffered with transient pains, mostly in her legs, though occasionally in her back.

On admission she was having from one to three painless bowel movements a day, and felt relieved but exhausted after movement of the bowels. Rectal examination showed the anus spastically contracted; no ulcers or growths were palpated within the rectum. Fluoroscopical examination of the chest was negative. The urine analysis was negative. The blood count on entrance showed a mild grade of anemia; hemoglobin 75, red cells 3,610,000; white cells 8700. Differential blood count showed: Small lymphocytes, 34.5 per cent; large lymphocytes, 4 per cent; large mononuclear, 1 per cent; transitionals, 4.5 per cent; polymorphonuclears, 55 per cent, and eosinophiles, 1 per cent. There were slight variations in size and shape. The alveolar CO_2 tension was 37. The stools were unusually bulky, whitish in color, pultaceous, yeasty, foamy, and had the odor of sour, spoiled cheese. Microscopic study showed some gram-positive and gram-negative bacteria, some bacillus coli and Monilia psilosis.

The feces and the scrapings from the tongue of the patient were plated in ordinary laboratory media (meat infusion + 2 per cent glucose) and on Sabouraud's medium (4 per cent glucose agar, + 2 acid reaction). On the ordinary laboratory media the colonies of the yeast were highly elevated, of a white creamy color, with a slight greenish tint, while on the Sabouraud's media the colonies were the same in appearance except somewhat more glistening and of a slightly mucoid consistency. The organisms from both media fermented dextrose, levulose, maltose, and sucrose with acid and gas formation. Lactose and mannite were not fermented. There was no reaction in litmus milk. In gelatin there was a typical inverted pine-tree growth without liquefaction. Morphologically the organism isolated from the ordinary laboratory media, after five days' incubation at 37° C., resembled ordinary yeast—granular, oval, measuring from 3 to 5 microns in greatest diameter. The organisms isolated from Sabouraud's media were round instead of oval, measuring from 5 to 10 microns, having a large brilliant nucleus and a small body with the appearance of a bacillus seen to be

actively floating around the nucleus. The organisms, isolated from ordinary laboratory media, when subcultured on Sabouraud's media, resembled each other morphologically. From this it seems evident that the organisms, when grown on the above named media, seemed to be distinct entities, but when grown on Sabouraud's media, the two resembled each other culturally and morphologically. Both the organisms corresponded in every respect, when grown on Sabouraud's media, with those described by Ashford.

An agglutination test was made on the organism isolated both from the feces and tongue of the patient. The organism when brought into contact with the patient's serum failed to give a satisfactory agglutination, but neither was Ashford's culture, used as a control, satisfactory in the agglutination test. The organisms seemed to settle out and clump very quickly. The tests were carried out macroscopically and microscopically. In every instance the controls showed the same clumping as those contained in the patient's serum.

An antigen was made from the organisms isolated from the stool and tongue scrapings of the patient. This antigen was used in the complement-fixation test, with a culture of Ashford's used as control. A positive complement-fixation reaction was obtained with both. The antigen made from the organisms isolated from the patient gave a somewhat weaker reaction with the water-bath incubation technic, but gave equally as strong positive complement fixation with the eighteen-hour ice-box fixation technic (Kolmer's technic). Complement fixations were made with all the antigens, with known normal serums, without any inhibition of hemolysis.

Using water bath (37.5° C.) incubation, the antigen made from Ashford's culture gave a slightly stronger reaction than did that made from our own culture, while, on the other hand, an eighteen-hour ice-box (10° C.) incubation, using Kolmer's new technic, complete inhibition was obtained with both antigens. Control tests were made on sera from several healthy individuals with negative results.

A rabbit was injected intravenously with 1 cc of a live suspension of the organism. The rabbit died forty-eight hours after the injection with symptoms of septicemia. The postmortem examination showed multiple pyemic abscesses in both kidneys. The liver was apparently normal, the spleen normal in size and somewhat of a greenish color. The suprarenal glands were normal. Direct microscopic examination of the heart blood and smear made from the kidney showed many active Monilia psilosis. These organisms were reisolated from the heart blood and kidneys on Sabouraud's culture media, and were found in the tissue of the kidney, of which slides were made and photographed (Figs. 1–3).

From these cultures a vaccine was prepared for the patient according to Colonel Ashford's method.

There were three basal metabolism studies made; one, by the Talbot method, gave a + 127; a second and third, by the Aub-Dubois method, + 55 and + 39 respectively. These findings were

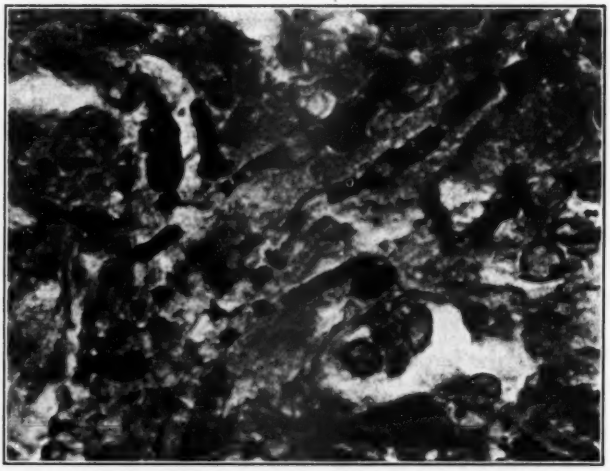


FIG. 1.—High-power microphotograph of Monilia psilosis as found in kidney of inoculated rabbit, autopsied.

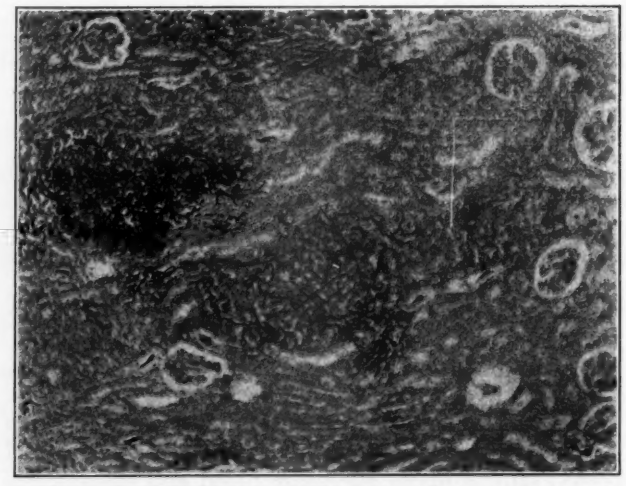


FIG. 2.—Low-power microphotograph of Monilia psilosis as found in kidney of inoculated rabbit, autopsied.

calculated on the basis of several published normal standards, the lowest rate only being reported, obtained with "The Normal Standard of Talbot" based on total calories for age.

As treatment the patient was given light tonic hydrotherapy,

such as alternating heat and cold to the spine, fomentations to the abdomen, footbath, wet hand rub or cold mitten friction, and the Ohmschlag or moist abdominal bandage was worn continuously,

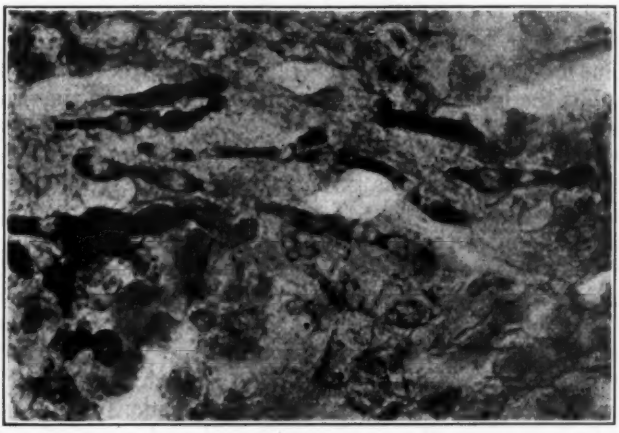


FIG. 3.—High-power microphotograph of Monilia psilosis as found in kidney of inoculated rabbit, autopsied.

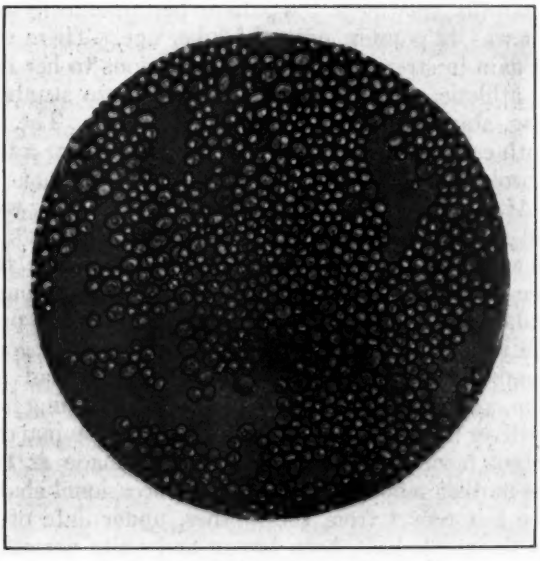


FIG. 4.—Organisms isolated from feces.

changing as often as dry. Cleansing enemas were given once a day, followed by a liquid culture of *B. Bulgaricus* and *B. acidophilus*, to retain. She was also given a culture of the same by mouth, about

3 ounces three times a day. The ulcers in the mouth were treated by applications of glycerin and phenol (2 per cent), 1 ounce of each.

She was put on a diet of acidophilus buttermilk and bananas, and after a short time was able to take a glass of buttermilk every hour and from 6 to 12 bananas a day. The bananas she took either baked or raw. The last few weeks under treatment she had some of the green leafy vegetables and an occasional baked potato, but the buttermilk and bananas still remained the principal part of her diet.

The patient was kept in bed at first, and even up to the close of her period of treatment was given two hours rest every afternoon.

During the last few weeks of treatment she was given iodin by mouth, beginning with 1 drop three times a day, increasing to 16 drops three times a day. In addition to this she was given autogenous vaccine every third day.

The child began to improve almost immediately. The bloating in the abdomen left her; she gained in weight; and the liver gradually decreased in size. Much improvement had already taken place before we succeeded in getting the vaccine made, but after a few weeks she was given the vaccine prepared and given as outlined above. She had apparently no reaction to the vaccine, but later on had localized abscesses at the seats of injection. At the close of about six months' treatment the patient had practically recovered. Her weight was 42 pounds, normal for her age. There was a proportionate gain in strength. The child previous to her illness had been very athletic, and was again doing trapeze stunts, walking and running, standing on her head, and so forth. The ulceration in the mouth came and went, healed for a few days or a few weeks, and then broke out again; but there has now been none for some months. After about three months' treatment the liver was normal in size and remained normal after that time, and the abdominal distention was very greatly diminished. At this time the stools, which were examined weekly, were still variable, though better formed and contained more bile, seldom showing the presence of the Monilia psilosis. The hiccoughs had been entirely controlled.

In December, eight months later, the patient had a recheck examination, and at this time we found her maintaining her normal weight, the liver normal size, very little if any abdominal distention, and the stool normal with the examination made at that time, though the mother reported still seeing an occasional characteristic stool. The last report from the mother, under date of April 19, 1925, says the stools have been brown and quite normal, and she has had no white or foamy stools since the first of January, 1925. The abdomen is still distended a little at night, but she maintains her normal weight and normal strength and activities.

Summary. A case of tropical sprue in a child, aged six years, including animal inoculation and isolation of Monilia psilosis both from the

patient and from the autopsied animal and photomicrographs of the parasites as stained in tissue, is reported, together with the treatment given and the results.

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THE SEVERE ANEMIAS OF PREGNANCY AND THE PUERPERIUM.

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The occurrence of severe and often fatal anemia in pregnancy and shortly after its termination was described by Walter Channing[1] of Boston in 1842. He distinguished this form of anemia from bloodless states due to hemorrhage and he had a theory to account for it. In one prophetic paragraph he discussed the dangers and possible benefits of the transfusion of blood.

Osler[2] classifies these anemias as follows: (1) Anemia secondary to postpartum hemorrhage; (2) severe anemia of pregnancy; (3) postpartum anemia; (4) acute anemia from puerperal sepsis. However, anemias resulting from hemorrhage or sepsis associated with pregnancy do not differ materially from those due to similar causes not so associated. It seems clearer, therefore, to restrict the definition so as to include only severe anemias beginning during or shortly after pregnancy, not due to obvious complications, but apparently resulting from the gravid state *per se*.

The writer has observed 17 cases that seem to come within this definition, and has classified them on the basis of the blood pictures. Whether the various types differ from one another etiologically cannot, of course, be stated at the present time. It may be that the difference is primarily one of severity, but each case in this series falls so definitely into one group or another, without intermediate forms, as to suggest that the difference is more fundamental.

Case Reports. Seven Cases with the Blood Picture of Secondary Anemia. Case I.—A Yiddish woman, aged twenty-four years, had acute arthritis in 1910, resulting in valvular heart disease. She remained somewhat pale and dyspneic, and these symptoms became severer as pregnancy advanced. Her fifth

baby was born in May, 1915. Delivery was complicated by slight hemorrhage; but there was neither sepsis nor fever. Five weeks later, she was pale, with a yellowish tinge. The heart was moderately enlarged and there was a definite presystolic murmur and a thrill. The liver and spleen were normal. The blood picture was that of a severe secondary anemia (Table I). She recovered from the anemia but died of mitral stenosis, in 1922.

CASE II.—An American woman, aged forty-two years, stated that she had "been yellow all her life," and had been pale for several months. Her eleventh child was born, at term, on March 10, 1923. The easy, low forceps delivery was not associated with any unusual loss of blood. Shortly after delivery she collapsed, and was sent to the hospital. On the fourth day she was "pale, with a buffy-yellow tinge," probably a bit cyanotic. There was no demonstrable enlargement of either liver or spleen. The blood (Table I) showed anemia of the secondary type. Her temperature remained normal. She improved somewhat and left the hospital against advice on the seventh day.

She was readmitted in January, 1925, eight months along in her twelfth pregnancy. She was moderately pale and somewhat puffy. Liver and spleen were normal. The anemia was less in degree but the same in type as before (Table I). Under ordinary hospital care and the administration of iron, she underwent marked improvement. She was delivered at term and soon after left the hospital against advice.

CASE III.—An American woman, aged twenty-eight years, gave a history of dyspnea and edema dating from the termination of her seventh pregnancy in 1921. On July 3, 1923, she was admitted in labor at full term, this being the eighth pregnancy in a period of nine years. Labor was precipitate and there was no hemorrhage. After delivery she collapsed, but recovered and went through her convalescence without fever or obstetrical complications. On the second day she was "pale, with a distinct yellowish tinge, the scleræ bluish." There was a systolic murmur, but no cardiac enlargement. The spleen was easily felt. The liver was normal. The blood (Table I) showed severe anemia of the secondary type. She was transfused on the seventh day, and discharged in excellent condition a month later. The murmur had disappeared, but the spleen was still palpable. In January, 1925, she was still well.

CASE IV.—An Italian woman, aged thirty-eight years, gave a story of malaria in Italy and of a severe hemorrhage following the birth of her fifth baby in 1912. After coming to this country in 1914, she had four normal deliveries and three abortions. One of the latter, in 1922, was accompanied by considerable bleeding. In May,

TABLE I.—ANEMIAS OF SECONDARY TYPE.

	Erythrocytes.	Leukocytes.

TABLE I.—ANEMIAS OF SECONDARY TYPE.

Case No.	Date.	Hemoglobin, per cent.	Erythrocytes.										Leukocytes.							Platelets, thousands per c.mm.
			Total, millions per c.mm.	Color index.	Achromia.	Anisocytosis.	Poikilocytosis.	Polychromatophilia.	Basic stippling.	Reticulocytes, per cent.	Nucleated cells per 100 w.b.c.		Total, thousands per c.mm.	Polyneutrophils, per cent.	Eosinophils, per cent.	Mast cells, per cent.	Lymphocytes, per cent.	Large mono. and transitionals, per cent.	Myelocytes, per cent.	
											Normo.	Meg.								
I	June 10, 1915	30	2.28	0.65	++	..	++	+	0	..	0	0	6.8	..	..	..	..	..	..	Normal.
II	Mar. 13, 1923	47	3.29	0.71	++	+	+	+	0	9.1	0	0	7.0	81	1	1	16	0	1	Decreased.
	Jan. 14, 1925	61	4.33	0.70	+	0	0	0	0	4.5	0	0	12.8	81	0	0	16	3	0	264
	Feb. 12, 1925	89	4.50	0.99	0	0	0	0	0	2.4	0	0	..	..	..	..	..	..	..	Normal.
III	July 5, 1923	31	2.34	0.66	+	++	++	++	0	5.6	0	0	11.0	82	0	0	17	1	0	156
	Aug. 9, 1923	50	4.20	0.60	+	+	+	++	+	5.3	0	0	5.0	45	8	0	35	12	0	112
	Nov. 3, 1923	82	5.74	0.71	..	..	..	..	..	1.4	0	0	11.0	69	3	1	23	4	0	240
IV	July 17, 1923	25	1.70	0.74	+	++	+	+	0	2.2	0	0	5.6	47	2	0	46	5	0	Normal.
	29, 1923	61	3.68	0.82																
	Nov. 11, 1924	56	4.04	0.69	++	+	+	0	0	3.0	0	0	7.7	58	1	0	28	13	0	Decreased.
	Jan. 13, 1925	75	5.00	0.75	..	..	..	..	..	6.6	..	..	14.0							
V	Apr. 11, 1924	39	3.38	0.57	++	+++	++	0	0	13.6	0	0	9.5	77	1	1	19	1	1	390
	21, 1924						Cesarean section and transfusion, 250 cc.													
	25, 1924	46	3.62	0.64	+	++	++	0	0	8.2	1	0	40.0	97	0	0	1	1	1	178
	May 1, 1924	35	2.90	0.60	..	..	..	..	..	7.0	..	..	10.6	80						
	22, 1924	52	4.80	0.54	+++	0	+	0	0	2.0	0	0	16.0	75	5	0	18	2	0	372
VI	Jan. 21, 1924	40	4.30	0.44	+	++	+	+	0	3.2	0	0	18.6	84	0	0	12	4	0	300
	Aug. 7, 1924	50	5.00	0.50	++	++	++	0	0	2.2	0	1	5.4	75	0	0	21	1	3	220
	22, 1924	60	5.80	0.52	+	..	..	..	..	..	..	..	17.0							
VII	Jan. 23, 1925	36	3.42	0.53	+	++	++	++	0	..	0	0	11.0	90	0	1	7	2	0	Normal.
	30, 1925	37	3.19	0.58	++	++	++	++	0	..	0	0	8.0	83	3	1	9	4	0	Abundant.
	Mar. 6, 1925	48	3.65	0.66	++	+	+	+	0	5.0	0	0	4.2	..	..	..	..	..	..	Increased.

1923, she gave birth to a healthy baby at term, without undue loss of blood. When seen, a month later, she was pale, with the swarthy tinge of her race. The heart and lungs were normal. Both liver and spleen were easily felt, the edge of the latter being noted as nodular. Although the Wassermann reaction was twice positive, there was no other evidence of syphilis. Pelvic examination was negative. There was no fever. The blood picture was that of a secondary anemia (Table I). The gastric contents after a test breakfast contained no hydrochloric acid; the total acidity was 25. She steadily improved and was discharged well.

CASE V.—An American woman, aged forty-two years, stated that she had been pale since a pelvic operation (appendix, left ovary and uterine fibroid) about 1910. In 1910 she had a nervous breakdown, accompanied by marked increase in pallor. She was admitted in April, 1924, late in her fifth pregnancy, with a history of increasing dyspnea and edema since the seventh month. She was pale, but not yellow, the scleræ slaty. The heart was normal in size and presented an obscure systolic murmur. The liver and spleen were normal. There were a few purpuric spots on the chest. The uterus was the size of an eight and a half months' pregnancy. The urine contained a faint trace of albumin, but no casts. The blood picture was that of a severe secondary anemia (Table I).

Cesarean section was done thirteen days later. The baby weighed seven and a half pounds, and did well. Although there was no excessive loss of blood, she was transfused with 250 cc of blood by the citrate method immediately after operation. Unfortunately the abdominal wound became infected, and convalescence was slow. The hematologic effects of this complication and the subsequent improvement are shown in Table I. She was still in good health in August, 1924.

CASE VI.—A Polish woman, aged thirty-two years, was admitted on June 9, 1924, in premature labor in the eighth month of her sixth pregnancy. She shortly gave birth to twins. There was no undue loss of blood. From the second to the fourth day there was slight fever, and on the sixth day a mild breast abscess appeared. When first seen by the writer, on the twelfth day, she was very pale, without yellowish tinge. There was a systolic murmur at the pulmonic area. The spleen was palpable, the liver normal. The blood (Table I) showed anemia of the secondary type. She improved slowly and was discharged at the end of six weeks. She was readmitted a fortnight later with acute polyarthritis, from which recovery was prompt. The systolic murmur persisted. The spleen was not palpable at this time. Her present condition is unknown. Both the premature babies died within a few weeks.

It is perhaps doubtful whether this case should be included in the

series, as the anemia was not carefully studied until after the onset of the breast abscess. Pallor, however, preceded the infection and the latter did not seem virulent enough to account for the degree of anemia that was present so early.

CASE VII.—An Irish woman, aged thirty-one years, was admitted on January 22, 1925, in labor at term, this being her first pregnancy and an illegitimate one. Pregnancy was normal, except for edema in the last two weeks. Delivery was spontaneous and there was no undue loss of blood. When seen, next day, she was moderately pale, the face somewhat puffy. Systolic blood pressure 160; diastolic 80. There was a slight systolic murmur, without cardiac enlargement. Spleen and liver normal. Urine normal. The blood was that of a severe secondary anemia (Table I). She was kept under observation for nearly two months. Although her general condition improved markedly, the blood figures rose so slowly that transfusion was advised. It was refused by the patient. The baby did well.

Comment. These 7 cases are classed together primarily because all showed the secondary blood picture, but the clinical resemblance is equally striking. All were afebrile except 2, and these had no fever until the onset of late septic complications. They were not very sick. The grade of anemia was severe enough, the average lowest hemoglobin being 35 per cent, but the anemia was not progressive, all began to improve at once after delivery or as soon as treatment was begun. Four were not transfused and, of the others, 2 were transfused only to expedite convalescence and 1 to make safer the necessary operative delivery. So far as is known none of them relapsed. Obviously the outlook is good.

A consideration of the individual histories in this group will show that nearly all the women were below par before the last pregnancy began, some of them giving clear stories of previous attacks of anemia, hemorrhage in preceding pregnancies or definite infections of severe type. This fact has also been noted by Adler.[19] Moreover, with the exception of Cases I and VII all had had numerous and frequently repeated pregnancies, the average number being 7.1.

Taking the patients' statements for what they are worth, symptoms began during pregnancy in 4 cases, and immediately after delivery in 2.

These cases are possibly related to the mild chloro-anemia which is seen so frequently in midpregnancy[10, 15] and in the puerperium[4] as to be classed as quasi-physiological by some authors. They are probably quite common, but the milder ones are not often referred to the internist for study.

EIGHT CASES WITH THE PERNICIOUS BLOOD PICTURE. CASE VIII.—An American woman, aged twenty-six years, gave a history of a

TABLE II.—ANEMIAS OF PERNICIOUS (VIII–XV) AND APLASTIC (XVI) TYPES.

Case No.	Date.	Hemoglobin, per cent.	Erythrocytes.											Leukocytes.							Platelets, thousands per c.mm.
			Total, millions per c.mm.	Color index.	Volume index.	Achromia.	Anisocytosis.	Poikilocytosis.	Polychromatophilia.	Basic stippling.	Reticulocytes, per cent.	Nucleated cells per 100 w.b.c.		Total, thousands per c.mm.	Polyneutrophils, per cent.	Eosinophils, per cent.	Mast cells, per cent.	Lymphocytes, per cent.	Large mono. and transitionals, per cent.	Myelocytes, per cent.	
												Normo.	Meg.								
VIII	Feb. 20, 1906	31	1.12	1.41	+	0	++	+	++	0	..	1	5	3.3	64	1.0	0	33	2.0	0	Normal.
IX	Apr. 7, 1906	10	0.73	0.67	..	0	++	++	++	++	..	1	2	10.2	63	1.5	0.5	29	5.0	1	Normal.
X	June 5, 1907	30	1.20	1.25	..	..	..	..	..	..	..	..	..	4.2							
	9, 1907	12	0.43	1.33	..	0	+++	++	+	++	..	0	0	5.4	78	0.5	0.5	18	3.0	0	
XI	Jan. 27, 1913	20	0.67	1.54	1.80	0	+++	+++	+++	++	..	3	20	7.0	69	0	0	26	2.0	3	
	Dec. 10, 1914	93	5.20	0.89	..	0	0	0	0	0	..	0	0	9.7	59	0	2.0	39	0	0	Normal.
XII	Nov. 8, 1919	12	0.59	1.00	−	0	++	+	+	0	4.0	0	2	3.1	34	0	0	62	4.0	0	
	Jan. 14, 1924	98	3.70	1.43	..	0	0	0	0	0	0.8	0	0	4.4	63	3.0	0	28	5.0	0	106
	Nov. 10, 1924	84	4.36	0.97	..	0	0	0	0	0	0.4	0	0	4.8	64	5.0	0	26	3.0	0	500
XIII	May 22, 1922	29	1.42	0.97	n.	0	+	+	++	0	..	0	5	2.0	73	0	0	22	5.0	0	136
	June 6, 1922	54	2.44	1.10	1.12	+	++	++	0	0	..	1	1	5.9	84	1.0	0	10	3.0	2	288
	July 10, 1922	80	3.76	1.07	1.06	0	+	+	0	0	..	0	0	6.1	75	3.0	0.5	14	7.5	0	336
XIV	Aug. 29, 1924	19	0.66	1.46	1.33	0	+++	+++	+++	+++	11.0	8	16	6.4	64	1.0	0	27	2.0	6	56
	Sept. 30, 1924	90	4.42	1.02	..	0	+	0	0	0	0.4	0	0	4.8	45	5.0	4.0	40	6.0	0	88
XV	Feb. 3, 1925	28	1.08	1.27	..	0	++	++	+	++	2.5	0	0	2.5	58	0	0	40	2.0	0	200
	5, 1925	49	1.60	1.53	..	..	..	..	..	..	3.0	..	..	2.6							
	11, 1925	48	1.72	1.41	..	..	..	..	..	..	2.8										
	Mar. 5, 1925	96	4.10	1.17	..	0	0	0	0	0	0.6	0	0	1.8	51	2.0	1.0	41	5.0	0	120
XVI	Nov. 1, 1922	20	0.78	1.25	−	0	+	+	+	0	0.4	0	0	2.6	48	1.0	0	49	2.0	0	64

seven months' miscarriage two years before I saw her. During this previous pregnancy she suffered from diarrhea and a sore mouth, which frequently bled, these symptoms persisting until two months before my examination. She was pale, but not at all yellow. The tongue was smooth, with red patches about its edge. There was a systolic murmur. Neither liver nor spleen was palpable. The blood picture (Table II) was typically pernicious. She was soon after delivered of a dead fetus and in a few weeks died of anemia.

CASE IX.—An Irish woman, aged twenty-two years, was seen when seven months along in her first, an illegitimate, pregnancy, early in which symptoms of debility began. The day before I saw here there was a chill and fetal motion had ceased. The color was "a transparent yellow, with marked cyanosis." There was a systolic murmur. The spleen was 2 inches below the costal border. She was "almost moribund." The blood (Table II) showed extreme anemia. The color index was so low as to suggest that this case should be classed among those with the secondary picture. But the hemoglobin was estimated by the Tallqvist method, which is not accurate for these low percentages. The leukocytosis is accounted for by the death of the fetus. In other essential respects, especially in the absence of achromia and the predominance of megaloblasts, the picture is clearly pernicious. A recent examination of the smear, now eighteen years old and badly faded, gives no reason to change this opinion. A few days after I saw here she was delivered of a dead fetus. She improved a bit and then died, apparently from anemia.

CASE X.—An Irish woman, aged thirty-four years, was delivered in February, 1907, without undue loss of blood. Vomiting, which had been somewhat excessive during pregnancy, persisted after confinement. In May she raised a small amount of blood. She was admitted on June 4, 1907. Although vomiting persisted, there was no hematemesis, and the guaiac test showed no blood either in the vomitus or stools. She was "pale, with slaty conjunctivæ." The liver was two fingers below the costal margin; the spleen was normal. The blood (Table II) showed a fairly typical picture of pernicious anemia. She died July 16, five months after her confinement.

CASE XI.—An American woman, aged twenty-eight years, was seen in consultation on January 27, 1913. Her mother was said to have died of "consumption of the blood." Her three pregnancies had been normal. Early in the last one she had erysipelas. She was delivered of a healthy full-term baby three months before I saw her. After her confinement debility and pallor continued to increase slowly. The temperature varied from normal to 100.° There was

no particular loss of blood at confinement, but from time to time afterward she passed small amounts of bright blood by rectum. She was "very pale, yellowish with a slightly waxy look." The heart area was normal, but there was a loud systolic murmur. The blood presented a typical pernicious picture (Table II). She soon began to improve and recovered completely. She has gone safely through two more pregnancies (1917 and 1919). The first one was followed by "slight anemia," the second was without incident. She is now (December, 1924) in excellent health.

CASE XII.—A woman, aged thirty-two years, presented a history of syphilis beginning about 1910, and from May, 1918, nearly up to the time of admission she was treated continuously at the Boston Dispensary with diarsenol, arsphenamin and salicylate of mercury. While under our care there was no evidence of this disease and the Wassermann reaction was negative. Her fifth pregnancy terminated, normally and at full term, on March 28, 1919, without undue loss of blood. Following confinement she suffered from an unusual and increasing sense of weakness. In August she became quite pale. Early in September she had tonsillitis followed by a crop of purpuric spots on the legs and arms, on account of which she was sent to us. She presented an extreme yellowish pallor. The spleen was palpable. There was a systolic murmur, without enlargement of the heart area. Otherwise physical examination was negative. The blood (Table II) showed anemia of extreme degree and with the pernicious picture.

Owing to a delay in obtaining a donor she was not transfused until October 12, by which time she was desperately ill. She then received 650 cc of blood, by the Kimpton-Brown method. After transfusion there was marked edema of the lungs and some fever. She remained unconscious or delirious for several days and then began to improve. Since her recovery she has gone through her sixth pregnancy without recurrence of the anemia. Today she is perfectly well, though the color index remains high.

CASE XIII.—An American woman, aged twenty-six years, was delivered of her second baby on May 4, 1923. Pregnancy had been uncomplicated except that in the later months there had been considerable pain in the right abdomen, and increasing pallor after the sixth month. She "went over her time" and labor was finally induced. Delivery was by low forceps. There was not much hemorrhage. The baby weighed 8 pounds and did well. On the day after confinement the temperature began to rise, reaching 102° at the end of a week. Although there was no evidence of sepsis except the fever, she was gently curetted. Fever persisted and pallor increased. The temperature chart is herewith depicted.

There was "marked straight pallor," and considerable pigmenta-

tion. The heart was rather large and there was a slight systolic and a doubtful diastolic murmur The liver was normal. The edge of the spleen was about 2 cm. below the costal margin. The blood picture was pernicious in type (Table II).

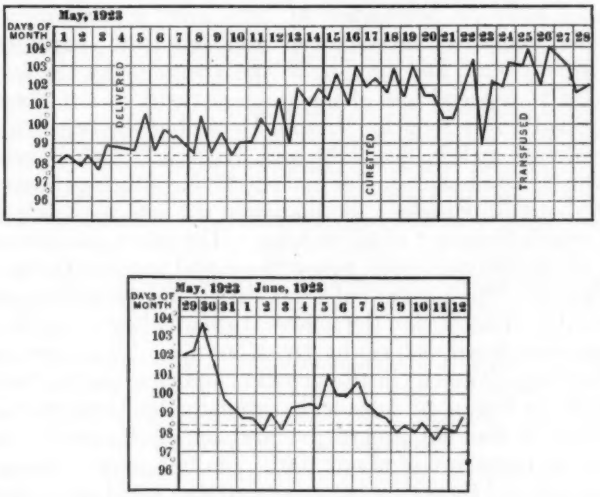

CHART I.—Case XIII. Temperature chart.

She was transfused (600 cc) by Dr. A. R. Kimpton, by the paraffined tube method, on May 26. Although the hemoglobin showed a rise of 19 per cent later in the day, there was little immediate clinical improvement. On the 29th she still had a temperature 103° and a pulse of 156, the mind was clouded and she looked badly. She became delirious and a few rales appeared in her right lower lobe posteriorly. By May 31, however, her temperature had fallen to normal and convalescence thereafter was rapid. The spleen was not felt after June 13. There has been no relapse.

CASE XIV.—An American woman, aged thirty-two years, gave birth to her first baby at term on July 23, 1924, without unusual loss of blood. Late in pregnancy she had several slight nosebleeds, but was not anemic. She continued to flow up to August 29. The temperature remained between 99° and 100° F. She was extraordinarily pale, with a slightly yellowish "sour-dough" tinge. There was no hemorrhage from the mucous membranes and none in the skin except a few pin-point spots on the upper front chest. The blood (Table II) presented a perfectly typical pernicious picture.

Within the next four weeks she was transfused four times by Dr. Kimpton, a total of about 2000 cc being given. On September 30, 1924, she was practically well, the color being about normal,

the spleen no longer palpable and the blood nearly up to the normal standard. She has remained perfectly well ever since, and the baby is normal.

CASE XV.—An American woman, aged twenty-seven years, had her second baby on November 30, 1924, after a pregnancy which was normal except for rather severe vomiting in the early months, and attacks of pain and tingling in the arms during the last two. There was no especial loss of blood at parturition, but three days later she had a sore mouth. In mid December she began to suffer from weakness, pallor, headache and dyspnea, which increased in severity up to admission, on February 2, 1925. During the six weeks she lost about 20 pounds. On admission she was very pale, with a muddy yellow tinge not at all striking. The heart was normal; the edge of the spleen was 4 cm. below the costal margin; the liver was just palpable. The blood (Table II) showed the pernicious picture.

On the day of admission the temperature was 103°. On February 4 she was transfused, 500 cc, by Dr. Kimpton. There was marked immediate improvement in the general condition and in the blood, and the fever began to subside. Although the improvement was maintained, it was not progressive and she continued to show an afternoon temperature of about 100°. On February 13 transfusion was repeated and thereafter improvement was rapid up to discharge on March 5.

Comment. In drawing a contrast between these cases with the pernicious picture and the previously described group, it is at once evident that we are dealing with a much more severe condition. Four occurred in pretransfusion days, and three of them died. All 4 of the more recent cases were transfused, and all recovered. My impression is that without transfusion the mortality in the whole group would have been 6 or 7 instead of 3.

At least 5 of these patients had more or less fever, and in some it was marked. The liver was palpable in 2 cases, the spleen in 5. The influence of repeated pregnancies was less marked than in the patients showing the secondary type of anemia, the average being 2.3 as contrasted with 7.1. Two cases delivered themselves prematurely, the fetus in each being dead. Six went to term, the 5 babies whose fate is known doing perfectly well.

As in the secondary group, it is difficult to date the onset of the anemia. In 3 it surely began before confinement, and probably rather early in pregnancy. In the other 5 it *seems* to have started only after parturition, at least neither patient nor their physicians suspected anemia earlier. Indeed in 2 instances it developed so slowly that the serious nature of the gradually increasing debility and pallor was not obvious for several months, and when the condition did become severe its causal association with pregnancy was lost sight of. The writer must confess that in Cases XI and XII

his own diagnosis at the time was pernicious anemia, and that the true nature of the disease did not strike him until months and years passed without the expected relapse. This slow, gradual onset after normal pregnancy and normal parturition was not seen in any of the cases showing the secondary blood picture.

A Case with the Aplastic Blood Picture. Case XVI.—An Irish woman, aged thirty years, was seen when three months along in her second pregnancy. For a month she had been complaining of debility, "fainting spells," and slight dyspnea, and there had been considerable morning vomiting. She was very pale, but not yellow; the scleræ slaty. The heart presented a loud systolic murmur and a suggestion of a presystolic. The liver edge could just be felt on deep inspiration; the spleen could not be palpated There were two small ecchymotic areas on the right shin, which she could not account for. The blood showed a fairly definite aplastic type of anemia (Table II).

She was given two transfusions with little or no effect As she had slight convulsions, possibly hysterical, at each attempt, only 250 cc of blood could be given. No effort was made to terminate the pregnancy. She died about three weeks later.

Comment. This case is classed as aplastic because of the great reduction of platelets and the absence of evidence of regeneration of the red corpuscles. The neutrophilic leukocytes are rather higher than is usual in outspoken aplasia, the absolute number being 1248 per c.mm. For this reason perhaps it is better called hypoplastic than aplastic. This picture is rarely seen in the anemias of pregnancy, but it is not unique, a somewhat similar instance having been reported by Jungmann.[6] In his case the aplasia was less striking than in mine, since erythroblasts were present, the neutrophiles were 7592 (73 per cent of a total leukocyte count of 10,400), and there were a few myelocytes. Jungmann's patient, who was seen at the end of pregnancy, was safely delivered, and afterward recovered.

An Atypical Case with Recovery after Splenectomy. Case XVII.—An American woman, aged thirty-one years, had endocarditis and pericarditis, with pallor and edema in 1918, during her second pregnancy. In August, 1923, during the seventh month of her third pregnancy these symptoms recurred. As the urine contained albumin and casts, her physician attributed the symptoms to nephritis. She was delivered, at eight months, on September 17, 1923. Very little blood was lost, and the baby did well.

On October 1, she was "extremely pale and transparent, but not yellow." There was a loud systolic murmur. The liver was slightly enlarged. The spleen was greatly enlarged, its lower border being

below the level of the umbilicus. On the legs were a few small ecchymoses, which she was unable to explain. Pelvic examination showed nothing remarkable. The temperature was 101° F. (see chart). The blood pressure was normal. The urine, on entrance, contained a minute trace of albumin and a few casts; several subsequent analyses were normal. The blood picture (Table III) will be discussed later.

During the next six weeks seven transfusions, totaling 3700 cc of blood, were given. By these vigorous measures it was possible to get the hemoglobin and red corpuscles up to fairly high figures. The temperature which was at first high and irregular, fell nearly to normal, and general improvement was manifest. On the other hand, as a glance at Table III will show, the anemia immediately

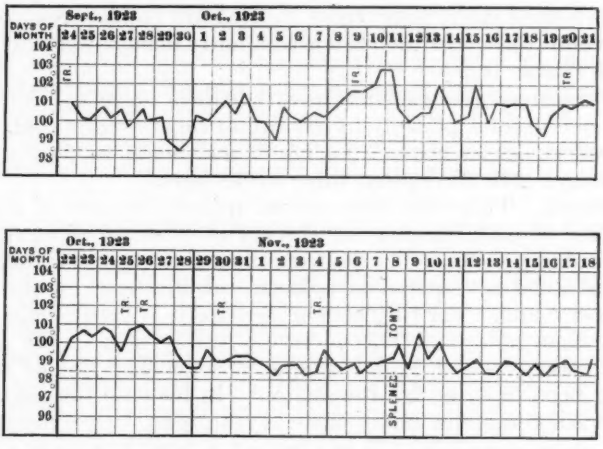

CHART II.—Case XVII. Temperature chart. (Tr. indicates dates of transfusions.)

and rapidly increased as soon as transfusions were stopped. This was not the result of hemorrhage, as the only loss consisted of very slight uterine oozing. There was no material change in the spleen.

Splenectomy was decided upon in view of the facts: (1) That hemolysis was very active, her serum being intensely yellow; (2) that the spleen was enormously enlarged, and (3) that there was marked fragility of the red corpuscles; hemolysis in hypotonic solutions of sodium chloride began at 0.575 per cent and was complete at 0.400 per cent (the normal figures are 0.425 and 0.325 per cent). The operation was performed by Dr. A. R. Kimpton on November 8. Without further transfusion the blood at once began to improve and within a week recovery seemed certain. Convalescence was, however, interrupted by phlebitis of both legs, lasting

TABLE III.—CASE XVII. ATYPICAL ANEMIA.

Erythrocytes.

Leukocytes.

TABLE III.—CASE XVII. ATYPICAL ANEMIA.

Case No.	Date.	Hemoglobin, per cent.	Erythrocytes.										Leukocytes.							Platelets, thousands per c.mm.
			Total, millions per c.mm.	Color index.	Achromia.	Anisocytosis.	Poikilocytosis.	Polychromatophilia.	Basic stippling.	Reticulocytes, per cent.	Nucleated rbc's per 100 w.b.c. Normo.	Nucleated rbc's per 100 w.b.c. Meg.	Total, thousands per c.mm.	Polyneutrophils, per cent.	Eosinophils, per cent.	Mast cells, per cent.	Lymphocytes, per cent.	Large mono. and transitionals, per cent.	Myelocytes, per cent.	
XVII	Sept. 24, 1923	16	0.73	1.07	0	+++	++	++	++	4.0	10	21	14.0	62	0	0	22	0	14	56
	24, 1923								Transfused,		500	cc.								
	Oct. 3, 1923	24	1.14	1.04	+	++	++	+++	+++	8.8	3	9	10.8	73	1	1	11	1	13	56
	9, 1923								Transfused,		500	cc.								
	15, 1923	17	1.36	0.63	..	..	..	..	..	5.2	..	..	1.8							
	20, 1923								Transfused,		500	cc.								
	24, 1923	15	0.81	0.94	0	++	++	+	+	..	..	..	3.4	..	..	..	..	..	..	Decreased.
	25, 1923								Transfused,		500	cc.								
	26, 1923								Transfused,		600	cc.								
	29, 1923	52	2.52	1.00	..	..	..	..	..	4.8	..	..	4.8	..	..	..	..	..	..	82
	30, 1923								Transfused,		500	cc.								
	Nov. 1, 1923	66	3.00	1.10	0	++	+	+++	+++	4.6	1	4	2.8	62	4	1	24	6	3	
	3, 1923	47	2.33	1.00	..	..	..	..	..	3.4										
	4, 1923	38							Transfused,		600	cc.								
	8, 1923	51	2.40	1.06	..	..	..	..	..	4.4	..	..	5.0	..	..	..	..	..	..	104
	8, 1923								Splenectomy.											
	9, 1923	44	2.50	0.88	0	+	+	++	+	4.4	95	11	12.8	89	1	0	8	2	0	72
	12, 1923	44	3.40	0.64	+	++	++	++	++	3.8	97	3	11.2	70	4	0	19	3	4	92
	16, 1923	55	3.13	0.87	..	..	..	..	..	1.6	44	3	13.0	64	7	1	19	0	9	272
	28, 1923	50	2.60	0.96	..	..	..	..	..	8.8	39	0	14.0	88	0	0	7	5	0	284
	Dec. 7, 1923	63	4.20	0.75	++	++	++	+	0	7.2	15	0	28.0	85	1	0	7	5	2	404
	Jan. 24, 1923	104	4.13	1.25	0	++	++	++	0	7.0	4	0	16.0	46	7	1	36	9	0	256
	Apr. 1, 1923	104	3.90	1.33	+	++	++	0	0	0	0	0	8.6	67	3	1	22	2	5	652
	Sept. 10, 1923	100	5.04	0.99	+	+	+	0	++	3.5	0	0	10.0	53	2	2	43	0	0	350

through December. On January 30, 1924, she was discharged well. In August, 1924, she had a mild attack of acute polyarthritis. She is now (March, 1925) perfectly well.

Dr. F. B. Mallory examined the spleen and reported as follows: "The spleen measures 22 x 12 x 9 cm. It is dark reddish-brown in color and firm in consistency. The cut surface is dark crimson and yields a moderate amount of pulp on scraping. Microscopically it shows congestion. The blood sinuses contain many undifferentiated cells, which are often grouped in small and large clumps. Each cell is surrounded by a moderate amount of basophilic cytoplasm. Mitoses occur in moderate numbers. All stages of differentiation between these cells and neutrophilic and eosinophilic leukocytes can be traced. Eosinophiles are very numerous and are located mostly in the pulp and often in clumps. No megacaryocytes or erythroblasts can be found. Diagnosis: Hypertrophy of spleen due to myeloblastic function."

This case is apparently unique. The blood picture, particularly the first two examinations recorded in the table, is difficult to classify. The numerous nucleated red corpuscles, with megaloblasts predominating, and the rather high color index suggest pernicious anemia. But the neutrophile leukocytosis is not thus explainable and the presence of numerous myelocytes in a patient with an enormous spleen brought up the question of leukemia. Hemolysis of fragile red corpuscles was obviously present. I believe that hemolysis was abnormally active and the presence of myelocytes is doubtless, in part at least, explained by the myeloblastic hyperplasia within the spleen. The apparent aplasia of the platelet-producing elements of the marrow, and later also of those producing leukocytes, was probably of the same nature as that seen in pernicious anemia—perhaps due to replacement of these cells by the intense hyperplasia of those producing red corpuscles.

The changes in the blood following splenectomy do not differ from those observed by many writers[13, 16] and they need not be discussed here.

General Comment. The *etiology* of these anemias is obscure. Some attribute them to the damage wrought on the hemopoietic organs by hemorrhage and infection. Some consider them an intensification of the "physiological chloro-anemia" of pregnancy.

Adler[19] believes that all the anemias of pregnancy occur in women who are predisposed, or who are already suffering from some other form of anemia, especially chlorosis, posthemorrhagic or secondary anemia, but rarely, if ever, from ordinary pernicious anemia. In such women, the added strain of pregnancy upon the blood-forming organs, results in pathologic conditions of greater or less severity and of varying types.

A more elaborate theory is that of Hofbauer. As quoted by

Rowland,[9] this is to the effect that a syncytial hemolysin is produced in the ectodermal cells of the chorion. Later an antihemolysin is formed in the maternal blood, which accounts for the disappearance of the slight anemia so frequently observed in the early months of normal pregnancy.[10] If such antibodies fail, a destructive anemia persists.

Carrel and Ebeling,[12] in a study of the growth of fibroblasts in the serum of old animals as compared with that of young ones, found evidence that the serum in adults contains some factor that inhibits cell growth. Galloupe and O'Hara,[11] basing their views upon this work, suggest that parturition may deprive the blood-forming tissues of some influence which they have been receiving from the fetus, and that a progressive anemia might result when the hemopoietic mechanism fails to compensate.

Finally, McQuarrie[17] has studied the isoagglutinins in the blood of newborn babies, with reference to the occurrence of toxemia of pregnancy in the mothers. Among the relatively small proportion of babies who have such isoagglutinins at birth, toxemia is 16.5 times as common where the maternal and fetal bloods are incompatible as when they are in the same group. It is possible that the hemolytic anemia of pregnancy, which has many points of resemblance to toxemia, may be connected with the same causes.

However suggestive these theories may be, they must be regarded for the present rather as leads for further study than as lucid and satisfactory explanations of the clinical facts.

Diagnosis and Relation to other Diseases. There are considerations both historical and hematological which invite a discussion of the relations between ordinary pernicious anemia and anemias of the pernicious type associated with pregnancy. But there are difficulties in the way of discussing with profit the fundamental relationship that may exist between two diseases in neither of which the etiology is known! In ordinary pernicious anemia everything points to a primary process of excessive hemolysis with a secondary hyperplasia of the marrow, compensatory in nature but abnormal in output. In the cases under discussion there is reason to suppose that the anemia is likewise hemolytic in origin and that the intense hyperplasia of the marrow is similar in nature. Further than this, existing evidence will not take us.

There is much confusion amongst writers on this subject, as regards both terminology and point of view. To many the similarity in blood pictures seems to justify the assumption that the "pernicious anemia of pregnancy" is identical with ordinary pernicious anemia. Adler,[19] however, clearly distinguishes between true pernicious anemia and "anemia graviditatis pernicioformis." He considers that they have nothing to do with one another, and that true pernicious anemia is very rarely seen in pregnant women.

From the clinician's standpoint the two diseases are as far apart

as the poles. In one the anemia is invariably fatal in the end, regardless of treatment. In the other nearly all cases will, with proper treatment, recover permanently. If the physician responsible for the lives of his patients will bear this one fact in mind, he need not lie awake nights worrying as to whether the two diseases are fundamentally distinct or merely the result of minor variations of the same underlying process.

Does ordinary pernicious anemia ever occur in pregnant or parturient women? The question could be answered in the affirmative by the demonstration of: (1) Cases in which a diagnosis of pernicious anemia in a nullipara has been established beyond reasonable doubt, and where pregnancy subsequently ensues, or (2) cases where anemia of the pernicious type is recognized during pregnancy and afterward runs a relapsing and remitting course with ultimate fatal termination and the postmortem lesions of pernicious anemia. I have never seen a case of either sort. Heim,[14] who recognizes the occurrence of pernicious anemia in pregnancy as a rare coincidence, reports one case in which conception apparently occurred during a remission, but exact data as to the condition of the blood previous to pregnancy are lacking. Indeed, in a doubtless incomplete survey of the literature, I have encountered not a single instance which can be accepted without reservation. This is rather remarkable, since ordinary pernicious anemia, although it occurs most frequently in women, as in men, during the fifth decade, is by no means rare in women of child-bearing age.

Anemia from ordinary obstetrical hemorrhages will seldom be confused with the type under discussion. The writer has seen blood pictures approaching the pernicious type as a result of successive severe hemorrhages, but ordinarily the picture, as soon as regeneration is fairly established, is clearly of the secondary type. A woman, after a postpartum hemorrhage, normally begins to improve rapidly within a few days. It is only where the anemia continues to progress, or where it is all out of proportion to the amount of blood lost, that doubt can arise. As hematologists occasionally see cases of obvious posthemorrhagic anemia not due to pregnancy, which are followed by such unusual results, their relationship to the conditions under discussion is questionable.

As many patients with anemia of pregnancy have heart murmurs and some have irregular fever, it is only natural that they should occasionally be mistaken for malignant or septic endocarditis. Particularly in the subacute bacterial form of endocarditis there may be notable enlargement of the spleen and severe anemia. The latter is almost always of the secondary type, with leukocytosis, as in other infections.[7] The association with pregnancy, the invariably negative blood cultures, the absence of embolic phenomena and the prompt recovery after transfusion with the disappearance

of fever, and usually of the murmurs, will make the differentiation clear.

It would seem almost inevitable that cases of postpartum anemia of the pernicious type should occasionally be mistaken for puerperal sepsis to the quite undeserved chagrin and humiliation of the obstetrician. The temperature may closely simulate that of sepsis and some degree of leukocytosis is not infrequently present, while the pallor of the patient is by no means incompatible with such a diagnosis. The obstetrician confronted with a case of apparent sepsis, in which pallor is a marked feature, will do well to make a thorough study of the blood. If the anemia is of the secondary type, with polymorphonuclear leukocytosis, it will point strongly toward sepsis. But if the picture is that of pernicious anemia, and particularly if there is also leukopenia, immediate transfusion should be done. If there is a prompt drop of temperature and progressive improvement after a single transfusion, infection as a cause is most improbable. In real septic infections transfusion has no such influence—albeit the operation is not infrequently performed with just this object in view.

Of course the future may show that perperal anemia is due to infection with some organism at present unknown, or that the disease is due to some influence not at present clear, of infection with known pyogenic cocci upon the hemopoietic mechanism. But at present such a hypothesis is pure speculation. And let me add that one's "index of skepticism" must indeed be low if he can believe that these terrible, acute anemias are the result of chronic foci of infection in teeth or tonsils, and can bring himself to hope for relief from their eradication.

Finally, the occurrence of similar types of anemia, of like severity, early in pregnancy, would seem sufficient proof of the existence of the condition entirely apart from septicemia in the ordinary sense of the word.

The *prognosis* is discouraging only if one has reference to the older literature. Experience seems to show that most of the cases with anemia of the secondary type will get well anyhow. With transfusion and other modern methods available, most of those with anemia of the more severe types will also recover, and may even go through subsequent pregnancies without recurrence. If the disease becomes severe early in pregnancy, the patient will probably abort. The babies, if born at term, generally do perfectly well, and the writer does not at all agree with Esch,[18] who believes that their outlook is poor.

Treatment. The milder cases, showing the secondary blood picture, will usually require only ordinary nursing care, with the use of iron and arsenic, "in which," Osler said in 1919, "I still have faith." As the writer's professional memory dates back to a period when

chlorosis was still an actuality, he has no lack of faith in the older pharmacopeial forms of mineral iron, seldom uses iron hypodermmically and does not attempt an increased ingestion of food iron. If mineral iron was absorbed from the alimentary tract in 1900, it is similarly absorbed in 1925. If the same striking effects are not seen today, it is not because the iron or the gut is changed, but because the disease is changed, we are not seeing forms of anemia in which iron therapy is so effective.

Transfusion has made an enormous difference in the outlook for these patients. Even the cases with the secondary blood picture may need it. When the pernicious picture is recognized they should have it without delay. The condition here is different from that in ordinary pernicious anemia. In the latter we know that transfusions will at best only defer the fatal termination. More will probably be called for later, and if one believes that their possible number is for any reason limited, one uses them economically. On the other hand, anemia of the pernicious type associated with pregnancy generally ends fatally without remission if left to itself, while most cases get well permanently if they are transfused. This being so, why wait?

Probably a single transfusion will suffice in the majority of cases, and recovery is sometimes marvelously prompt. Obviously something more has been accomplished than merely supplying more red corpuscles upon which the destructive factor may continue to work. The destructive factor is itself thrown out of gear, or the normal relationship between production and destruction is reëstablished. If one transfusion does not do it, the operation should be repeated until it *does*. Seldom will one find himself in the unpleasant situation so common in ordinary pernicious and aplastic anemia of having to decide when to withhold his hand and let the inevitable happen.

The writer prefers the Kimpton-Brown method,[5] in which paraffined tubes are used without citrate or other anticoagulant, particularly where platelets are low and there is a tendency to hemorrhage. It is a ticklish procedure, however, and requires skill and experience. If these are not available, the citrate method should be used. In the absence of evidence that small amounts are equally valuable, at least 500 cc should be given.

Splenectomy, although it was attended with most brilliant results in one of my cases, is not advocated as a routine procedure. It was undertaken here only because repeated transfusion had failed, and certain recognized indications were present.

In cases originating early in pregnancy the question of emptying the uterus arises. In mild cases of the secondary type it is surely justifiable to let pregnancy proceed. Probably Rowland is in general correct in saying that "any case bad enough to require trans-

fusion is bad enough for termination of pregnancy." This question has caused some discussion amongst writers on the subject.[18] It should be said that the unfavorable results were recorded mostly by earlier writers, who did not have at their command the free use of transfusion. The proper course must depend upon the merits of the individual case, having reference to the type and severity of the anemia, the stage of pregnancy and the viability of the fetus.

Finally there is the question regarding future pregnancies. In one of the cases reported by Galloupe and O'Hara[11] anemia recurred with increasing severity in several successive pregnancies, and these writers refer to similar cases in the literature. On the other hand my Case XII has been through a subsequent pregnancy without recurrence and Case XI has been through two. A similar instance is mentioned by Osler. One's personal equation will enter largely into the question. It is fair, however, to bear in mind the hopeful prognosis of the condition today, as compared with the past.

Summary. 1. Seventeen cases are recorded of anemia occurring in pregnancy and the puerperium, all of severe grade. The blood picture may be that of secondary anemia, pernicious anemia, or aplastic anemia, or it may be atypical.

2. All 7 cases with the secondary blood picture recovered. Transfusion seems a question of expediency rather than of necessity.

3. Eight cases presented the pernicious blood picture. Of 4 not transfused 3 died. Four recovered after transfusion.

4. One case of the aplastic type died in spite of transfusion.

5. A highly atypical case recovered, after splenectomy, repeated transfusions having been unsuccessful.

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NONFATAL CARBON MONOXID POISONING.

Report of a Case.

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Practically all the cases of carbon monoxid poisoning hitherto reported have died very shortly after exposure to the gas, and have been so severely intoxicated as to produce serious and profound lesions in the brain. It is of interest, therefore, to report a case of proven carbon monoxid poisoning in which exposure was not sufficient to cause death, but in which the symptoms corresponded to the anatomical distribution of the lesions found in more severe cases. By means of this case also a closer correlation of clinical and pathological findings is possible, for a careful study of the former in a case which has not been killed by the gas, will reveal where and to what extent certain brain areas are affected in the less severe cases, and whether these cases show a progressive degeneration in the areas affected. Aside from this, the progress of a case which has been sufficiently injured by carbon monoxid to produce definite symptoms of brain destruction without causing death is in itself a matter of interest, particularly since very few such cases have been put on record.

Report of Case. History. Mr. H. Y., a young man aged nineteen years entered the Philadelphia Orthopedic Hospital on November 14, 1924, complaining of numbness in his left face and difficulty with his speech for two weeks. The family history was entirely negative. The patient worked as an installer of furnaces. He was entirely well until three weeks before entrance, or until October 20, 1924. At this time he was engaged in cleaning the boilers in a large plant, while the fire was still going. He inhaled a good deal of coal gas in the procedure, and was at work for forty-five minutes. One hour after the job was completed he complained of numbness of his right leg and of uncontrollable hiccoughs. The hiccoughs persisted, despite attempts to stop them, for seven or eight hours. About five hours after the exposure his right arm felt as if it were asleep. His right leg was still numb. On awakening the next morning his entire right side felt numb, including the right side of his head. He was never unconscious, but he had headache and dizziness from the onset of his illness. The headache had disappeared two days after the onset of his trouble, but his dizziness persisted for some time. The numbness in his right side persisted without abatement for one week, but then gradually grew less,

until at the time of entrance into the hospital it was but slightly apparent. From the beginning he had weakness in his right arm, such as to cause him to drop things readily. About one week before entrance he found that he could not open his right eye very widely and that his speech seemed thick. He could not articulate his words well, and twisted them up.

EXAMINATION. At the time of entrance he was dull and almost stupid. The general physical examination was entirely negative. The heart and lungs were normal. Blood-pressure: 128 systolic, 80 diastolic. The cranial nerve examination was entirely negative. The pupils were dilated but reacted well to light and in convergence. The fundi showed definite congestion of the retinal vessels, but no papilledema. All the other cranial nerves reacted normally. In the motor system one found a definite weakness of the right upper extremity, and a slighter degree of weakness of the right lower extremity. The dynamometer readings gave values of 40 kg. with the right hand and of 70 kg. with the left hand. A moderately coarse tremor of the right hand was elicited, and definite but not severe incoördination with the usual tests. There was also definite incoördination of the right lower extremity. In the Romberg position a definite unsteadiness was apparent. The gait was ataxic with dragging of the right foot, the right leg swinging out in walking and the right foot dropping. The speech was slurring with the usual test phrases. The reflexes of the upper extremities showed more active reflexes on the right side. The patellar and Achilles reflexes were hyperactive on both sides. No pathological reflexes were elicited: no Babinski, Oppenheim or clonus. There was a definite dysphagia, but no loss of swallowing.

LABORATORY EXAMINATION. Examination of the blood revealed: Red cells, 5,230,000; white cells, 9000; hemoglobin, 85 per cent, and a normal differential count. The blood Wassermann was negative. Blood sugar was 111.1 mg. per 100 cc. Blood-urea nitrogen was 13.3 mg. per 100 cc, and the nonprotein nitrogen was 22.6 mg. per 100 cc. Two spectroscopic examinations showed no carbon monoxid spectrum. A chemical examination of the blood revealed a trace of carbon monoxid. One month later, on discharge, this was not present.

COURSE OF ILLNESS. The patient was in the hospital from November 14, 1924, to December 16, 1924, a period of about one month. During his stay in the hospital the striking feature of the case was the great fluctuation in the symptoms and signs which the patient showed. After the third day in the hospital the difficulty in swallowing disappeared. The gait was for a time more ataxic than on entrance, but gradually improved until on discharge he walked quite well but he still had a definite ataxia. His reflexes varied a good deal. The patellar reflexes remained hyperactive, but on some days the left was more active than the right and *vice versa*. He developed a slight but definite rigidity of his right lower limb,

but this too disappeared before discharge. At times his arms felt weak, at times strong. They had regained a good deal of power before discharge, so that dynamometer readings showed 130 kg. with the right hand and 125 kg. with the left. He showed a good deal of emotional instability, laughing spontaneously with no provocation. His writing even up to a few days before discharge was extremely tremulous, and shortly before discharge he developed again numbness in his left side.

The patient showed no definite and steady improvement in any one way during his stay in the hospital, but rather a tendency to clear up in one respect only to have old symptoms and signs recur. His condition upon discharge may best be described probably as merely a mitigated state of his condition upon entrance.

Comment. While there has been much careful work on the pathology in the brain following carbon monoxid poisoning, there have been very few observations on the nonfatal cases of carbon monoxid poisoning. Stewart[1] reported a case of poisoning with carbon monoxid which showed bilateral softening in the corpus striatum and involvement by softening and hemorrhage of the deeper layers of the cortex, of the cerebellum, and of other parts of the brain. While most of the damage was in the corpus striatum, there was definite evidence of injury in other portions of the brain. Stoeper[2] found lesions in the cortex and cerebellum, with very decided softening in the lenticular nucleus. Ruge,[3] in 1922, made a very interesting contribution. He studied 12 cases of carbon monoxid poisoning and concluded that softening and changes in the vessels occurred typically in the lenticular nuclei in carbon monoxid poisoning. In cases of moderately severe poisoning he found that fatty degeneration occurs in the ganglion cells twenty-four hours after poisoning, together with small hemorrhages into the perivascular spaces. After two days there occurs softening in the lenticular nuclei, but this is not well marked until four or five days after the injury. Ruge believes that injury to the nerve cell is the primary process, and that the thrombosis which is so commonly found in carbon monoxid poisoning follows upon this. Others have reported on the softening of the lenticular nuclei which is so commonly found in this condition, without, however, pointing out that there is at the same time a diffuse, wide-spread parenchymatous degeneration throughout the whole cerebrospinal axis. This was pointed out by Stewart,[1] by Ruge,[3] Pineas,[4] Poellchen[5] and others.

It is difficult of course to correlate the findings in a case of carbon monoxid poisoning as reported in our patient in whom the injury was so slight, with the pathological findings as described in the literature. It is of more importance probably to record the findings as indicative of a slight degree of poisoning. This alone can be scientific when no postmortem proof is at hand. On the other hand, a study of the findings in our case reveals the fact that while

there were symptoms and signs of involvement of the lenticular nuclei, not all the findings could be explained on the basis of pathology in this area though most of them are explainable on this basis. The weakness of the upper extremity, the rigidity—moderate to be sure—in first one lower extremity and then the other, the increased reflexes in the lower extremities, together with the difficulty in swallowing and the stiff gait, suggest an interference with pyramidal tract conduction and with the bulbar nuclei. Very likely the amount of injury which was produced was probably no more than Ruge describes as taking place twenty-four hours after moderately severe poisoning, namely, a fatty degeneration in the ganglion cells; or even less than this may have occurred. Certainly no very severe injury to the lenticular nuceli could have been possible for the signs were never very marked. Particularly interesting was the shifting of physical signs, of weakness first in one arm, then in another, and of stiffness in alternate legs. The difficulty which the patient had in swallowing was a real one, and often resulted in the inability to swallow liquid foods. This had practically completely disappeared on discharge.

The unsteadiness of gait and the incoördination of the arms and legs might be explained by the presence of a peripheral neuritis which has been shown by Wilson and Winkelman[6] to be present in cases of carbon monoxid poisoning. On the other hand, there never were signs of a peripheral nerve inflammation, and the type of asynergia which the patient showed was definitely of a cerebellar type. One might venture the opinion that they were due to involvement of the cerebellum either by punctate hemorrhage, or by involvement of the ganglion cells. Headache, which has been described by Forbes, Cobb and Fremont-Smith[7] as an early symptom in carbon monoxid poisoning, was present but a very short time and was not very severe. These authors have pointed out also that carbon monoxide poisoning in the experimental animal is followed by cerebral edema. They do not state, however, how long the edema persists, and what may be its results, besides headache.

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THE EFFECT OF SPLEEN EXTRACT AND BONE MARROW ON THE BLOOD PICTURE IN PULMONARY TUBERCULOSIS.

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The work done by Leake and Evans, of the University of Wisconsin, on spleen extract and bone marrow in the treatment of secondary anemia seems to furnish a tangible means with which to improve the blood picture in the various types of secondary anemias. In a recent article[1] they describe the results obtained by them in the treatment of anemia by the oral administration of spleen extract and bone marrow in capsule form, principally in general medical and surgical cases. They[2] believed that there must be some reserve in the body for the blood constituent and felt that stimulation of the bone marrow would cause a rapid production of erythrocytes and a corresponding increase in the hemoglobin content, the bone marrow being the reservoir for the cellular elements of the blood.

Fisher and Snell,[3] of the National Military Hospital, Milwaukee, recently published a report of 28 cases whose anemias were treated with this preparation. Twenty-two of these cases showed definite improvement in the blood picture.

Reference can be made to a recent article[4] published by the writer in which a series of 23 cases, suffering from active pulmonary tuberculosis were treated, 21 of whom showed a definite improvement in the blood picture.

A desire to confirm these results lead to the selection of another group of 23 cases, using the blood picture as the index for making selections. These were all cases of active pulmonary tuberculosis. Spleen extract and bone marrow* was administered to these patients in capsule form three times daily, a half hour before meals after a control period of one month. Weekly counts were made on each patient during the one-month period of control and also during the two-months period of treatment. Only a moderate amount of improvement resulted during the control period; but during the period of treatment a marked rapid rise in the hemoglobin percentage and red cells was obtained.

All hemoglobin determinations were made with a Bausch and Lomb colorimeter and the Max Levy hemocytometer used in counting the cells. One technician† was engaged in the work, making the percentage of error constant.

As objective criteria of improvement the rule used by Leake and Evans[5] was followed. They state that "If the hemoglobin percentage did not improve by 5 points nor the erythrocyte count by 250,000

* The spleen marrow used in this investigation was prepared by the Wilson Laboratories, Chicago.

† I wish to express my appreciation of the careful technical work done by our laboratory technician, Miss Anna E. Ryan.

cells, the case was classed as showing no improvement. An increase in the hemoglobin percentage between 5 and 10 points and in the red blood cells between 250,000 and 500,000 placed the case in slightly improved class. If the hemoglobin percentage rose from 10 to 15 points and the erythrocyte count from 500,000 to 1,000,000 cells, the case was noted as moderately improved. An increase in a patient of over 15 points in hemoglobin percentage and over 1,000,000 in the red cell count was considered as markedly improved."

TABLE SHOWING EFFECT OF TREATMENT ON THE BLOOD PICTURE.*

Patient.	Degree of disease.	Period, weeks.	R.b.c. per cu. mm.	Hemoglobin, per cent.	
1 . .	Far adv.	1	4,520,000	82	
		2	4,610,000	86	
		3	4,720,000	90	
		4	4,830,000	90	
		5	5,080,000	90	
		6	5,210,000	95	
		7	5,240,000	95	
		8	5,320,000	95	
		9	5,410,000	95	
		10	5,630,000	95	
		11	5,620,000	95	
		12	5,650,000	100	Markedly improved.
2 . .	Far. adv.	1	2,950,000	50	
		2	3,020,000	55	
		3	3,020,000	57	
		4	3,020,000	58	
		5	3,500,000	62	
		6	3,470,000	65	
		7	3,930,000	70	
		8	3,900,000	75	
		9	3,970,000	75	
		10	3,990,000	75	
		11	4,000,000	75	
		12	4,140,000	75	Markedly improved.
3 . .	Far adv.	1	4,930,000	80	
		2	5,020,000	85	
		3	4,840,000	85	
		4	4,870,000	85	
		5	5,070,000	90	
		6	5,470,000	95	
		7	5,540,000	95	
		8	5,500,000	95	Moderately improved and left institution against advice.
4 . .	Mod. adv.	1	4,890,000	80	
		2	4,830,000	80	
		3	4,700,000	78	
		4	4,700,000	78	
		5	4,700,000	80	
		6	4,810,000	80	
		7	4,810,000	80	
		8	5,050,000	80	
		9	5,050,000	89	
		10	5,220,000	95	
		11	5,380,000	95	
		12	5,520,000	95	Moderately improved.

* The beginning of treatment, which was always after the fourth week, is indicated by a dash line.

Patient.	Degree of disease.	Period, weeks.	R.b.c. per cu. mm.	Hemoglobin, per cent.	
5 . .	Far adv.	1	2,980,000	50	
		2	3,020,000	55	
		3	3,160,000	55	
		4	3,280,000	57	
		5	3,360,000	58	
		6	3,380,000	58	
		7	3,610,000	60	
		8	3,610,000	60	
		9	3,110,000	70	
		10	4,120,000	70	
		11	4,190,000	70	
		12	4,230,000	75	Markedly improved.
6 . .	Far adv.	1	3,840,000	60	
		2	3,790,000	60	
		3	3,610,000	60	
		4	3,550,000	60	
		5	3,480,000	60	
		6	3,490,000	60	
		7	3,520,000	65	
		8	3,580,000	65	
		9	3,710,000	65	
		10	3,750,000	65	
		11	3,980,000	65	No improvement; left institution against advice.
7 . .	Far adv.	1	3,280,000	55	
		2	3,000,000	55	
		3	3,330,000	55	
		4	3,520,000	56	
		5	3,320,000	50	
		6	3,330,000	50	
		7	3,380,000	55	
		8	3,390,000	55	
		9	3,400,000	60	
		10	3,440,000	60	
		11	3,490,000	60	
		12	3,500,000	60	No improvement.
8 . .	Far adv.	1	4,950,000	80	
		2	4,840,000	78	
		3	4,890,000	80	
		4	4,890,000	80	
		5	5,260,000	85	
		6	5,550,000	95	
		7	5,590,000	95	
		8	5,640,000	100	
		9	5,680,000	105	
		10	5,670,000	105	
		11	5,650,000	110	
		12	5,650,000	110	Markedly improved.
9 . .	Far adv.	1	4,370,000	80	
		2	4,330,000	77	
		3	4,330,000	80	
		4	4,330,000	75	
		5	4,720,000	75	
		6	4,700,000	75	
		7	4,530,000	75	
		8	4,700,000	80	
		9	5,040,000	80	
		10	5,050,000	80	
		11	5,070,000	85	
		12	5,070,000	85	Moderately improved

Patient.	Degree of disease.	Period, weeks.	R.b.c. per cu. mm.	Hemoglobin, per cent.	
10 . .	Far adv.	1	4,850,000	84	
		2	4,780,000	83	
		3	4,780,000	83	
		4	4,780,000	82	
		5	5,040,000	80	
		6	5,260,000	85	
		7	5,230,000	90	
		8	5,250,000	95	Slightly improved; left institution without advice.
11 . .	Mod. adv.	1	3,970,000	70	
		2	4,140,000	75	
		3	4,370,000	78	
		4	4,380,000	80	
		5	4,510,000	80	
		6	4,700,000	80	
		7	4,950,000	85	
		8	5,170,000	88	
		9	5,180,000	90	
		10	5,220,000	90	
		11	5,340,000	90	
		12	5,520,000	95	Markedly improved.
12 . .	Far adv.	1	4,400,000	75	
		2	4,450,000	75	
		3	4,540,000	75	
		4	4,610,000	76	
		5	4,770,000	75	
		6	5,440,000	85	
		7	5,620,000	85	
		8	5,610,000	88	
		9	5,580,000	90	
		10	5,580,000	90	
		11	5,510,000	95	
		12	5,650,000	95	Markedly improved.
13 . .	Far adv.	1	4,820,000	82	
		2	4,750,000	75	
		3	4,750,000	73	
		4	4,790,000	75	
		5	4,810,000	78	
		6	5,150,000	80	
		7	5,170,000	83	
		8	5,180,000	85	
		9	5,190,000	87	
		10	5,290,000	90	
		11	5,310,000	90	
		12	5,500,000	95	Moderately improved.
14 . .	Mod. adv.	1	4,390,000	80	
		2	4,600,000	80	
		3	4,610,000	83	
		4	4,620,000	80	
		5	4,640,000	80	
		6	5,100,000	85	
		7	5,130,000	85	
		8	5,220,000	85	Moderately improved and left institution against advice.

Patient.	Degree of disease.	Period, weeks.	R.b.c. per cu. mm.	Hemoglobin, per cent.	
15 . .	Far adv.	1	4,730,000	80	
		2	4,440,000	78	
		3	4,430,000	75	
		4	4,430,000	75	
		5	4,680,000	75	
		6	5,150,000	80	
		7	5,130,000	80	
		8	5,160,000	85	
		9	5,200,000	85	
		10	5,280,000	85	
		11	5,380,000	85	
		12	5,540,000	90	Slightly improved.
16* . .	Far adv.	1	4,170,000	80	
		2	4,090,000	80	
		3	4,410,000	80	
		4	4,470,000	80	
		5	4,660,000	85	
		6	4,660,000	85	
		7	4,950,000	88	
		8	5,160,000	90	
		9	5,160,000	90	
		10	5,270,000	92	
		11	5,270,000	92	
		12	5,290,000	95	Markedly improved.
17 . .	Far adv.	1	5,100,000	85	
		2	5,030,000	82	
		3	5,010,000	80	
		4	4,930,000	80	
		5	4,960,000	80	
		6	5,440,000	85	
		7	5,490,000	90	
		8	5,540,000	90	
		9	5,510,000	95	
		10	5,510,000	95	
		11	5,670,000	95	
		12	5,670,000	100	Moderately improved.
18 . .	Far adv.	1	4,580,000	80	
		2	4,460,000	80	
		3	4,460,000	80	
		4	4,770,000	80	
		5	4,980,000	90	
		6	5,150,000	90	
		7	5,140,000	90	
		8	5,210,000	90	
		9	5,250,000	90	
		10	5,400,000	90	
		11	5,460,000	95	
		12	5,460,000	95	Moderately improved.
19 . .	Far adv.	1	4,630,000	80	
		2	5,040,000	90	
		3	5,030,000	90	
		4	5,240,000	90	
		5	5,330,000	90	
		6	5,520,000	90	
		7	5,540,000	90	
		8	5,620,000	95	Markedly improved;
		9	5,610,000	98	left institution
		10	5,680,000	100	against advice.

* Female.

Patient.	Degree of disease.	Period, weeks.	R.b.c. per cu. mm.	Hemoglobin, per cent.	
20 . .	Mod. adv.	1	4,210,000	80	
		2	4,600,000	85	
		3	4,690,000	85	
		4	4,760,000	85	
		5	4,820,000	87	
		6	5,110,000	90	
		7	5,140,000	95	
		8	5,160,000	95	
		9	5,160,000	100	
		10	5,450,000	100	
		11	5,570,000	100	
		12	5,610,000	100	Markedly improved.
21 . .	Mod. adv.	1	3,790,000	70	
		2	4,000,000	80	
		3	4,360,000	80	
		4	4,610,000	84	
		5	4,640,000	85	
		6	5,180,000	88	
		7	5,380,000	90	
		8	5,380,000	90	
		9	5,560,000	100	
		10	5,590,000	105	
		11	5,620,000	110	
		12	5,740,000	110	Markedly improved.
22 . .	Far adv.	1	5,020,000	87	
		2	5,040,000	90	
		3	5,080,000	90	
		4	5,090,000	90	
		5	5,410,000	90	
		6	5,500,000	95	
		7	5,520,000	95	Slightly improved; left institution against advice.
23 . .	Mod. adv.	1	4,050,000	80	
		2	4,330,000	80	
		3	4,460,000	83	
		4	4,890,000	88	
		5	5,260,000	90	
		6	5,550,000	92	
		7	5,550,000	97	
		8	5,620,000	100	
		9	5,630,000	105	
		10	5,670,000	110	
		11	5,690,000	110	
		12	5,790,000	110	Markedly improved.

There seems to be a variance of opinion among tuberculosis clinicians relative to the blood picture in tuberculosis. However, many clinicians have observed that a simple anemia is present in the majority of active cases of pulmonary tuberculosis; and it is quite generally conceded that in patients suffering from complications such as tuberculosis of the kidney or bladder, a definite secondary anemia is often present.

Pottinger[6] has observed that the hemoglobin and red cells are usually diminished and present the picture of a simple anemia. Red cell counts and hemoglobin estimations were made on 261 cases at this institution and of the entire group only 38, or 14 per

cent showed the hemoglobin to be 90 per cent or above and the erythrocytes 4,800,000 or above.*

Schlomovitz[7] in a recent publication showed conclusively by a comparison of relative blood cell volume in tuberculosis, that many a real anemia exists where apparently none was present. Fishberg[8] has also noted that the hemoglobin percentage and red cell count is occasionally low; but believes that the condition is apt to occur most often in the early and late stages of the disease.

All data pertaining to the clinical course of the cases reported in this paper have been omitted, as the main object of this report is to shown the effect of spleen extract and bone marrow upon hemoglobin and red cell production.

Thus far there are no data appearing in the literature pertaining to the effect this preparation has upon the clinical course of tuberculosis; and it is believed that observations of the effect of this preparation upon the clinical course of the disease should be made.

It would be interesting to read the reports by independent workers on the results obtained with this preparation in the treatment of tuberculosis.

Summary. 1. Twenty-three cases of active pulmonary tuberculosis are reported; 2 showed no improvement in the blood picture; 3 were slightly improved; 7 moderately improved and 11 were markedly improved, making a total of 21, or 91 per cent improved.

2. Spleen extract and bone marrow will definitely increase erythrocyte and hemoglobin production.

3. Further study of the use of this preparation in tuberculosis is indicated.

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* From the laboratories of the Oak Forest Tuberculosis Hospital.

A REPORT OF SIX CASES OF PYELITIS IN THE NEWLY-BORN INFANT.

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Pyelitis in the newly-born infant has generally been considered an uncommon disease. As far back as 1876, Huttenbrenner called attention to pyelitis in infants, but he referred more to older infants and young children. Since then, Escherich, Trumpp, Holt and others have reported pyelitis in older infants and young children. Göppert, in 1908, found pyelitis to be rare in the first three months of life. In 106 cases, 63 occurred in the first year of life and only 6 in the first three months. He estimates that about 1.2 per cent of his patients have pyelitis.

Pyelitis is probably much more prevalent in female than in male infants. Escherich, Göppert, Helmholz, Grulee and Abt agree that the percentage of occurrence in females is high, ranging from 70 to 100. Schwartz concludes that actual bacilluria is twice as prevalent in girls as in boys. Helmholz believes, however, that the ratio in newly-born infants is more nearly equal.

It is probable that all cases of pyelitis are caused by bacteria, which gain entrance to the mucosa and adjacent urinary parts as a result of a lowered resistance. The bacteria most commonly noted are Staphylococcus pyogenes aureus and albus, streptococcus, colon bacillus, typhoid bacillus, tubercle bacillus, and pneumococcus. In 1894, Escherich believed that the sole causative organism was B. coli and even named the condition "colecystitis." Helmholz reports 45 cases, 36 girls and 9 boys; 36 cases showed B. coli, 1 staphylococcus, 2 pneumococcus, "1 B. lactis aërogenes, and 3 bacilli of the intermediate group of Gärtner." Hoppe believes that a vast majority of pyelitis cases are caused by B. coli. The fact that the majority of these pyelitic infections in older infants and children are girls having a B. coli infection suggests a contamination of the urethra with fecal material from a soiled diaper.

The following cases of pyelitis in newly-born infants have been observed.

Case Reports. Case I.—Infant, L., male. This infant developed a temperature of 103.6° F. twelve hours after birth. This symptom was accompanied by restlessness and crying. At this time the urine obtained under as nearly as possible aseptic conditions showed 100 pus cells per c.mm. and a pure culture of Staphylococcus pyogenes aureus. During the second day, in spite of a 10-ounce

water intake the symptoms remained the same, with the temperature rising to 104° F. The blood count was hemoglobin 85 per cent, erythrocytes 5,200,000; leukocytes 12,600. Blood cultures from both mother and child were negative. A catheterized specimen showed 120 pus cells per c.mm. and a pure Staphylococcus aureus culture. The water intake was emphasized and the child alkalinized. The temperature gradually subsided and the pus-cell count diminished until upon the seventh day the temperature was normal and the pus-cell count was only 2, with a negative culture. The symptoms entirely disappeared until the twenty-first day when there was a recurrence with symptoms of fever—100° to 101.6° F., restlessness and a urine cell count of 30, showing a pure culture of Staphylococcus aureus. The blood showed 12,000 white cells. These symptoms disappeared in four days and the child is now four months old and apparently normal.

CASE II.—Infant, M., female. This infant had a sharp rise of temperature to 102.6° F. on the third day. This was accompanied by restlessness and crying. Several catheterized specimens of urine showed pus cell counts from 100 to 150 and pure cultures of nonhemolytic streptococcus. The blood count was hemoglobin 90 per cent, erythrocytes 5,200,000, leukocytes 11,400. Blood cultures were negative. This child was put on treatment, and the findings steadily decreased and showed normal at the twelfth day. This child is now six months old. A good water intake has been maintained and the urine kept mildly alkalinized. There has been no recurrence.

CASE III.—Infant, C., male, was premature two months; weight, $3\frac{1}{2}$ pounds; incubator baby. There were apparently no abnormal findings. This infant developed a sudden temperature of 104.4° F. on the third day. The baby was very restless. The urine showed 250 pus cells per c.mm. and a pure culture of B. coli. Death occurred on the fourth day.

The following cases are from the service of Dr. Grulee at Presbyterian Hospital, Chicago:

CASE IV.—Infant, T., female. This infant suffered a rise in temperature on the third day to 100.6° F. accompanied by vomiting, which was at times projectile. In the absence of any physical findings, the urine was obtained under as nearly as possible aseptic conditions. The findings were 100 pus cells per c.mm. and a pure culture of Staphylococcus aureus. Repeated cultures gave the same results. The temperature subsided during the fourth day but there was a sudden elevation on the ninth day. The child left the hospital on the eleventh day. No further record is available.

CASE V.—Infant, O., male. This infant had an elevation of temperature on the third day to 100.6° F. He was regurgitating food, was very restless and cried a great deal. On the fifth day, the urine showed 400 pus cells per c.mm. and a nonhemolytic streptococcus. The symptoms of crying and vomiting continued although there was some improvement. When the child left the hospital on the tenth day, the urine still contained many pus cells and the cultures showed nonhemolytic streptococcus. No additional record is available.

CASE VI.—Infant, W., female. There was an elevation of temperature on the first day to 100° F. This slight fever continued nine days and was accompanied by regurgitation of food, vomiting and lifelessness. A urinalysis on the fourth day showed 3000 pus cells per c.mm. with a culture of B. coli. The blood count showed hemoglobin 85 per cent and leukocytes 16,500. These symptoms together with the urine findings were only moderately improved when the child left the hospital on the tenth day. No additional history is at hand.

The urine samples from these patients were secured either by catheterization or by using antiseptic precautions. Schwartz states that cultural growths from specimens obtained with sterile precautions are only slightly more frequent than those obtained by catheterization and that the latter is desirable but not essential. Kretschmer believes noncatheterized samples are inaccurate.

In this series, the first symptom noted in each case was an elevation of temperature ranging from 99° to 104° F. No local symptoms could be found on thorough examination, but in 4 of the cases there were rather marked restlessness and crying as if the infants were in distress. In 3 of the cases, regurgitation of food was noted. In none of the 6 cases was there any diarrhea, a condition so often reported preceding or attending pyelitis in older infants. Two of the patients were rather languid although at the same time irritable.

Contrary to the accepted finding that the large majority of the cases of pyelitis in older infants are females, this series in newly-born infants tends to strengthen the statement of Helmholz that in newly-born infants the proportion is nearly equal. Of the 6 infants, 3 are male and 3 female. The causative bacteria in this series were twice B. coli, twice nonhemolytic streptococcus, and twice Staphylococcus aureus. This suggests that the overwhelming majority of B. coli infections such as is found in older infants is not present in the newly-born. Grulee has told me personally that he had 1 case of pyelitis in a newly-born infant showing a pure culture of Bacillus pyocyaneus.

That the fever usually has its onset about the second or third day, also suggests the possibility of an intra-uterine infection, or infection

at the time of birth. Case I might be interpreted as a congenital pyelitis. The leukocyte counts ranged from 11,000 to 16,000 figures which are not necessarily high for a newly-born infant.

The treatment used in this series was the one often followed. Sodium citrate, sodium bicarbonate, or equal parts of each were given with large amounts of water. With the exception of Case III, which was a premature baby, these patients all responded to this management. Their symptoms were relieved and the urine showed a rapidly decreasing pus-cell count. Practically all authorities agree that the one most important factor second to a correct diagnosis is the proper irrigation of the urinary passages through an increased intake of water. This may be given by mouth, by rectum, by hyperdermoclysis, intraperitoneally, or even by the intravenous route. In this series, it was not necessary to resort to any method other than by mouth. It is probably true that it is impossible to make the urine sufficiently alkaline so that it inhibits the growth of the B. coli. The curative properties of the alkaline medication may be due to the general alkalinization and the diuretic effect.

Summary. 1. The incidence was the same in the two sexes in this series.

2. The infecting organisms in this series were Staphylococcus aureus, a nonhemolytic streptococcus and B. coli, each in 2 cases.

3. The time of onset suggests an invasion by the bacteria at the time of birth in most instances.

4. Case I suggests a congenital infection.

5. Leukocyte counts ranged from 11,000 to 16,000.

6. Blood cultures were negative.

7. These patients responded to alkalies and large quantities of water.

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THE PRACTICAL VALUE OF NEUTRAL RED AS A TEST FOR GASTRIC SECRETORY FUNCTION.*

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Previous to 1923, methods of testing the function of the stomach were based largely upon the administration of a test meal and the estimation of the quantity of acid and ferment in the stomach. At about this time several investigators in Europe attempted to test the stomach's ability to excrete certain dyestuffs. More recently others have advocated the use of dyes as a test for gastric function.

Neutral red as a clinical test for gastric function was suggested by Finkelstein[1] in the course of his investigations on the gastric excretion of dyes used in testing the function of the liver. Of 8 dyes tested, he found that only neutral red was excreted in the Pawlow pouch of a dog after subcutaneous injection. Fuld[2] had previously noted that neutral red appeared in the Pawlow pouch of a dog after the dye was introduced into the stomach proper. Later Glaessner and Wittgenstein[3] applied this observation clinically in a series of 40 cases. Four cubic centimeters of a 1 per cent solution of neutral red was injected by them intramuscularly and the appearance time of the dye in relation to various states of gastric acidity noted. The appearance time in hyperacid cases was from seven to eight minutes, in normal cases from ten to fifteen minutes, in hypoacid cases twenty to sixty minutes, and in anacid cases the dye was not excreted. They also noted that the gastric mucosa showed a distinctly stained area around the pylorus, and expressed the opinion that the acid cells were principally concerned with the dye excretion. Saxl and Scherff[4] investigated particularly the gastric excretion of methylene blue. They observed that the entire gastric mucosa was equally stained by the dye following its intravenous injection. These workers further noted that neutral red was secreted to a greater extent by the stomach than methylene blue. Neutral red injected into the peritoneum of a rat was not eliminated by any particular type of gastric cell, although the pyloric segment was more intensely stained with dye than the fundus.

Hirbayashi,[5] in experimenting with gastric cannula dogs, found

* Read before the Association of American Physicians at Washington, D. C., May 7, 1925.

that the rate of excretion of neutral red depended upon the degree of stomach secretion as a whole, and that local lesions of the mucosa delayed and lowered the excretion of the dye. The stomach continued to eliminate dye after the hydrochloric acid was completely suppressed by silver-nitrate solution.

With the idea of attempting to ascertain the clinical adaptability of this method of testing gastric function, this work was undertaken. We have realized for some time the inadequacy of the fractional gastric analysis for determining accurately the presence of achylia gastrica. In this condition especially, the information gained from such analyses with regard to the secretory function of the stomach is not altogether reliable. Therefore, with the hope that the excretion of neutral red might prove a welcome addition to our diagnostic armamentarium in cases of this type, particularly the borderline cases of hyposecretion and anacidity, we have carried out this test in a number of patients, showing varied gastric conditions.

TABLE I.—APPEARANCE TIME OF NEUTRAL RED IN STOMACH FOLLOWING INTRAMUSCULAR INJECTION OF 40 MG. OF DYE.

Case No.	Acidity.	Appearance time of acid by fractional analysis.	Appearance time of dye. Minutes.	Group average.
I	Hyper.	Present in fasting stomach	18	
II	Hyper.	Present in fasting stomach	30	
III	Hyper.	Present in fasting stomach	7	
IV	Hyper.	Present in fasting stomach	11	23 min.
V	Hyper.	Present in fasting stomach	15	
VI	Hyper.	30 to 40 min.	50	
VII	Hyper.	Present in fasting stomach	20	
VIII	Normal	Present in fasting stomach	30	
IX	Normal	Present in fasting stomach	17	
X	Normal	Present in fasting stomach	9	
XI	Normal	Present in fasting stomach	15	$14\frac{1}{4}$ min.
XII	Normal	Present in fasting stomach	5	
XIII	Normal	Present in fasting stomach	12	
XIV	Hypo.	45 min.	45	
XV	Hypo.	15 "	32	
XVI	Hypo.	45 "	30	
XVII	Hypo.	15 "	27 25	
XVIII	Hypo.	Present in fasting stomach	30	
XIX	Hypo.	60 min.	71	
XX	Hypo.	20 "	45	
XXI	Hypo.	45 "	45	
XXII	Hypo.	45 "	20	32 min.
XXIII	Hypo.	45 "	12	
XXIV	Hypo.	Present in fasting stomach	20	
XXV	Hypo.	Present in fasting stomach	12	
XXVI	Hypo.	45 min.	60	
XXVII	Hypo.	Present in fasting stomach	10	
XXVIII	Hypo.	Present in fasting stomach	6	
XXIX	Hypo.	15 min.	15	
XXX	Hypo.	45 "	60	

Appearance Time in the Stomach following Intramuscular Injection. In the first series of cases tested, the following technic was employed: The patient-reported after a twelve-hour fast. An ordinary gastro-duodenal tube was passed into the stomach and the residuum withdrawn. Four cubic centimeters of a 1 per cent solution of neutral red (40 mg.) were injected intramuscularly into the gluteal region. Water was given by mouth and a steady drip established from the duodenal tube. The first faint pink color in the gastric contents thus obtained, was recorded as the appearance time of the dye.

Thirty cases were examined in this way. They were divided into 3 subgroups according to the degree of acidity: hyperacid, normacid and hypoacid (Table I). The appearance time of the dye in 7 cases of hyperacidity ranged from seven to fifty minutes with an average of twenty-three minutes. In the normacid group of 6 cases the appearance time was from five to thirty minutes with a group average of fourteen minutes. Seventeen cases of subacidity had an appearance time of from six to seventy-one minutes, averaging thirty-two minutes to the group. The hypoacid cases as a group show a greatly delayed appearance time of the dye. The normacid stomachs secrete the dye more rapidly than the hyperacid group. The small number of cases in these last 2 groups make any definite conclusion as to the relative appearance time for these groups impossible.

Quantitative Intramuscular Method. An estimation of the amount of dye secreted by the stomach in two hours was attempted on a series of cases. The method used was first suggested by Davidson of Boston, who is working with neutral red in cases of pernicious anemia.

Using the same amount of dye, injected in the same manner as given above, and with the patient lying on the left side, 50-cc quantities of water were introduced into the stomach through the tube at fifteen-minute intervals. The water was drained into a series of bottles over a period of two hours.

The appearance time of the dye was noted. The quantity of liquid obtained from the stomach during each fifteen-minute interval was then subjected to a colorimetric determination as follows:

Each fifteen-minute return was diluted to 100 cc with water and poured into a test tube of large diameter. Standards were made by dissolving accurately weighed amounts of neutral red in water. The dilutions ranged from 1 to 8,000,000 to 1 to 100,000, representing 0.00013 gm. to 0.001 gm. respectively in 100 cc of water. These dilutions were placed in standard size large caliber test tubes for comparision. The gastric juice does not alter the color of the dye in any way and accurate comparisons are possible. The standards should be freshly prepared every six weeks.

Twenty-two cases are included in this quantitative series (Table II). They have been classified according to the degree of gastric

acidity. Five hyperacid cases had an average elimination of 0.0676 mg. of dye in two hours after the injection of the 40 mg. of neutral red. One of these cases had practically no elimination, although a hyperacid curve was obtained from the gastric analysis. Only 3 cases having normal acidity were tested; the group average was 0.1313 mg., or twice that of the hyperacid cases. The average secretion for the group of low acid cases was 0.0387 mg., considerably below either of the other groups. The dye appeared as a faint trace in 6 cases. These cases had extremely low acidities or very much delayed appearance time of hydrochloric acid secretion following the test meal. The greater proportion of dye was eliminated during the first hour.

TABLE II.—QUANTITATIVE ELIMINATION OF NEUTRAL RED IN THE STOMACH FOLLOWING INTRAMUSCULAR INJECTIONS OF 40 MG. OF DYE.

Case No.	Degree of acidity.	Neutral red excreted in 2 hrs., mg.	Group average acid excretion, mg.
I	Hyper.	Estimation not possible	
II	Hyper.	0.0705	
III	Hyper.	Very faint trace	Hyper., 0.0676.
IV	Hyper.	0.1035	
V	Hyper.	0.0963	
VI	Normal	0.0598	
VII	Normal	0.2401	Normal, 0.1313.
VIII	Normal	0.0598	
IX	Hypo.	Faint trace	
X	Hypo.	0.0307	
XI	Hypo.	Faint trace	
XII	Hypo.	0.030	
XIII	Hypo.	0.112	
XIV	Hypo.	0.143	
XV	Hypo.	Faint trace	Hypo., 0.0387.
XVI	Hypo.	Faint trace	
XVII	Hypo.	0.0809	
XVIII	Hypo.	Faint trace	
XIX	Hypo.	0.0083	
XX	Hypo.	Faint trace and bile	
XXI	Hypo.	0.0663	

The following conclusions are warranted from this study of the quantitative technic following the 40 mg. intramuscular dose.

1. Only 0.25 per cent of the neutral red introduced was obtained from the stomach in the normacid cases. The quantity is so infinitesimal that a quantitative estimation of the amount is of little value.

2. The hyperacid group has a lower dye excretion than the normal acid group. The same result was found in testing for appearance time only.

3. It is only in the markedly reduced acidities that the test seems to be of value.

Intravenous Injection of 125 mg. of Dye. The small amount of dye excreted following a 40-mg. dose injected intramuscularly led us to try larger amounts of dye intravenously.

Dr. John A. Kolmer very kindly tested out the toxicity of neutral red on rabbits. He reported that it was well borne in the dose of 0.1 gm. per kilogram of body weight. He found that 0.2 gm. would kill the animal immediately, and reported 0.140 gm. as the maximum tolerated dose. If human beings were of equal susceptibility this would mean that an individual weighing 70 kg. could stand about 9.8 gm.

Five hundred milligrams were injected intravenously in 3 cases. The return was instantaneous and the amount of dye was sufficient to color each return a deep red. The patients suffered untoward effects, notably cough, dyspnea, vomiting and generalized discomfort. Three cases were given 250 mg., and the dye elimination was still considered excessive. It was found that 125 mg. of dye was the most suitable dose. The technic followed was the same as that referred to under the quantitative intramuscular method, except that 125 mg. of neutral red dissolved in 5 cc of sterile water were injected into a vein followed by 5 cc of normal salt solution.

Appearance Time following Intravenous Method. The appearance time of the dye following the injection of 125 mg. of dye intravenously was recorded in 19 cases (Table III). Three cases of hyperacidity had an average appearance time of four minutes; six minutes was the group average for 3 normacid cases. Thirteen cases of hypoacidity (not including achylia) had an average appearance time of fourteen minutes after the injection. The intravenous injection of the dye produces a more rapid appearance time than the intramuscular injection (Table I).

As a rule the higher the acidity, the more rapidly the dye appeared in the stomach. This is not specificially true in each instance, for example, in 5 cases of low acidity the dye was present in less than eight minutes. Two of these cases had an appearance time of four minutes; the average for the hyperacid group. All of the normal and hyperacid cases had dye in the stomach in eight minutes or less after injection. Two cases classified as hypoacidity but having gastric enzyme had dye in the stomach in four and seven minutes (Cases XIII and XVII). It is obvious that the appearance time of dye in the stomach does not depend solely upon the degree of acidity nor the appearance time of acid following a test meal, and cannot be depended upon as a test for gastric secretion.

Quantitative Elimination: Intravenous Method. Three hyperacid stomachs after the intravenous injection of 125 mg. of dye, eliminated on an average 2.393 mg. of dye in two hours (Table III). The average excretion for 3 normacid cases was 1.699 mg. of dye. Thirteen cases of hypoacidity had an average elimination of 0.353 mg. In this series there was a crude ratio maintained between the degree of acidity and the amount of dye excreted by the stomach. This ratio is more constant than the ratio between the appearance time of the dye and the degree of acidity. The normacid cases

excreted only 1.2 per cent of the dye injected in two hours. This represents a very small percentage of dye excretion by the stomach. That the dye is largely eliminated by other organs than the stomach is obvious. Consequently, little reliance can be placed upon any quantitative method of testing the secretory function of the stomach by this dye.

TABLE III.—APPEARANCE TIME AND QUANTITATIVE ELIMINATION OF NEUTRAL RED IN THE STOMACH FOLLOWING INTRAVENOUS INJECTIONS OF 125 MG. OF DYE.

Case No.	Acidity.	Appearance time of acid in fractional gastric analyses.	Appearance time of dye, min.	Dye eliminated in 2 hours, mg.	Average appearance time, min.	Average dye, mg.
I	Hyper.	Fasting	4	2.717	4	2.393
II	Hyper.	Fasting	4	3.486		
III	Hyper.	Fasting	4	0.976		
IV	Normal	Fasting	8	1.434	6	1.699
V	Normal	Fasting	5	0.644		
VI	Normal	Fasting	5	3.019		
VII	Hypo.	Fasting	15	0.230	14	0.353
VIII	Hypo.	None	8	1.38		
IX	Hypo.	45 min.	16	0.283		
X	Hypo.	Fasting	7	0.018		
XI	Hypo.	None in 45 histamin	12	0.751		
XII	Hypo.	45 min.	5	0.221		
XIII	Hypo.	None; histamin	7	0.025		
XIV	Hypo.	30 min.	4	0.797		
XV	Hypo.	None	45	Trace		
XVI	Hypo.	None	35	Trace		
XVII	Hypo.	None	4	0.289		
XVIII	Hypo.	None	6	0.596		
XIX	Hypo.	None	15	Trace		

Cases of True and Questionable Achylia Gastrica. A series of 20 cases suspected of having achylia gastrica were examined (Tables IV and V). Eleven of these cases failed to show dye in the stomach following either the intravenous or the intramuscular injection, or both (Table IV). Two cases were examined by the intravenous method only, 5 by both methods, and 4 by the intramuscular method. Five of them had no secretory response following an injection of histamin. The remaining cases were not examined by the histamin method, but repeated gastric analyses over a considerable period of time consistently demonstrated the absence of both acid and enzyme. In Case VIII, both methods were carried out. By the intravenous method an appreciable amount of flocculent material was present in the second bottle (thirty to forty-five

minutes extraction). When the acid was added to this sediment it was colored a faint pink. The sediment microscopically was found to consist of cellular matter probably exfoliated from the duodenum. Two cases (I and III) had a trace of bile regurgitated into the stomach in one of the extractions. These bottles containing a trace of bile also contained a small amount of dye, after adding hydrochloric acid.

TABLE IV.—THE RESULTS OF INTRAMUSCULAR AND INTRAVENOUS INJECTIONS OF NEUTRAL RED IN TRUE ACHYLIA GASTRICA.

Case No.	Acid and enzymes in fractional analyses.	Gastric secretion after histamin injections.	Dye found after intramuscular injections of 40 mg. neutral red.	Dye found after intravenous injections of 125 mg. neutral red.
I	Negative	Not done	None	None
II	Negative	Negative	None	None
III	Negative	Not done	None	None
IV	Negative	Not done	None	None
V	Negative	Not done	None	None
VI	Negative	Negative	None	None
VII	Negative	Negative	None	None
VIII	Negative	Negative	None	None
IX	Negative	Negative	None	None
X	Negative	Negative	None	None
XI	Negative	Negative	None	None

TABLE V.—THE RESULT OF INTRAMUSCULAR AND INTRAVENOUS INJECTIONS OF NEUTRAL RED IN QUESTIONABLE AND TRUE ACHYLIA GASTRICA.

Case No.	HCl in fractional gastric analyses.	Rennet in fractional gastric analyses.	Gastric secretion after histamin injections.	Dye found after intramuscular injections of 40 mg. of neutral red.	Dye found after intravenous injections of neutral red.
I	Negative, 1; present, 2	Negative, 1; present, 2	Not done	Trace	
II	Repeatedly absent	Present, 1	Acid present	Trace	Dye appeared in 7 min.; small amount.
III	Negative, 1; low, 2	Negative, 1; present, 2	Acid present	Moderate amount	Dye appeared in 5 min.; normal amt.
IV	Repeatedly absent	Repeatedly absent	Acid and rennet present	None	Dye appeared in 12 min.; moderate amount.
V	Repeatedly absent	Repeatedly absent	Acid negative; rennet present	None	Dye appeared in 8 min.; moderate amt.
VI	Absent	Present	Not done	Not done	Dye appeared in 15 min.; trace.
VII	Repeatedly absent	Present	Not done	Not done	Dye appeared in 6 min.; moderate amt.
VIII	Repeatedly absent	Negative, 1; present, 2	Not done	Not done	Dye appeared in 4 min.; moderate amt.
IX	Absent	Negative	Not done	Not done	Dye appeared in 35 min.; trace.

Table V includes a series of 9 very instructive cases. They were considered to be achylias at some time previous to the neutral red test. In 3 cases (IV, V and IX), both acid and enzyme were repeatedly absent after fractional gastric analyses. Cases IV and V had either acid or enzyme after histamin injection. The intramuscular injection of 40 mg. of dye failed to cause excretion by the stomach in these 2 cases. Following the injection of 125 mg. of dye intravenously, a considerable amount of dye appeared in the stomach. These 2 cases cannot be classified as instances of true achylia gastrica, because of response to histamin. The intramuscular dose of 40 mg. proved insufficient to produce neutral red excretion. The intravenous method is superior to the intramuscular technic in suspected cases of achylia gastrica. The neutral-red test, however, cannot be held superior to the injection of histamin for the same purpose. Indeed, it is less satisfactory because of the possibility of dye regurgitation into the stomach from the duodenum in achylia gastrica cases. In 4 cases in which histamin caused acid and enzyme response, dye was extracted from the stomach following the injection of 125 mg. intravenously. Case V had enzyme but no acid, even after histamin injections, yet dye appeared following intravenous injection. This rather excludes the acid cells as the only excretory cells for neutral red.

Excretion of Dye by Other Organs. Every case upon which the neutral-red test was performed was instructed to expectorate saliva into a basin. The saliva was examined for dye by adding hydrochloric acid, and it was found to be invariably absent. At the end of the two-hour test, the tube was removed and the patient asked to urinate. The urine was deeply colored by dye in every instance. In the cases in which little or no dye was obtained from the stomach, more dye was secreted in the urine. The dye was also present in the stools following neutral-red injections.

Animal Experiments. A short time after the clinical work on neutral red was started, it was obvious that animal experiments were necessary in order to determine the exact location of neutral red in the body following injection. It was decided to determine if possible, which cells in the stomach secreted the dye, and also what other organs took part in its elimination. These experiments were carried out in the Pathological Laboratories of the Graduate School of Medicine of the University of Pennsylvania, through the kind assistance and coöperation of Dr. Fred Boerner.

EXPERIMENT 1. Ten milligrams of neutral red were injected into the ear vein of a rabbit after the animal's abdomen had been opened and the pylorus clamped to prevent regurgitation of bile into the stomach. The animal was killed thirty minutes after injection. Dye could not be found in any of the viscera of the rabbit. It was found necessary to use a much larger dose in order to cause sufficient staining of the cells.

EXPERIMENT 2. The same procedure was carried out using 100 mg. of dye. The animal was killed after forty minutes. The dye was distinctly perceptible in the urine and bile from the gall bladder. The kidneys, liver and small intestines were stained with dye. The salivary glands did not contain dye. The stomach mucosa was stained a deep pink color throughout. There was a zone extending up from the pylorus for a distance of about 2 inches, which was more deeply stained and also a concentric ring of deep red about ½ inch below the cardia. The duodenal mucosa was stained to a lesser degree than the mucosa of the stomach. Frozen sections were prepared from various levels of the stomach. Sections taken from all parts of the stomach showed dye distributed in the mucosa and submucosa. There was no difference in the degree of staining in any particular group of cells. All cells seemed to be stained equally. In spite of the large amount of dye injected the cells appeared only slightly tinted after frozen section.

EXPERIMENT 3. The same procedure was carried out on a cat weighing 8 pounds. The organs resembled grossly those of the rabbit with regard to the dye content with one exception. The first 12 inches of the mucosa of the small intestines were injected much deeper with dye than the stomach mucosa. The difference in degree of staining was marked. The duodenum just below the pylorus was a deep red for a distance of 6 inches, a lighter yellowish red for 6 inches which merged into a pink tint. The stomach mucosa was a pink tint throughout. The cat proved to be an unsatisfactory animal for experiment due to its frightened condition before and after injection. It was thought possible that the animal may have had a temporary suppression of gastric secretion due to fear. Although comparative histologists do not describe any difference in cell distribution in the cat, it was deemed advisable to test the excretion of neutral red in an omnivorous animal as well.

EXPERIMENT 4. One hundred milligrams of neutral red were injected into the ear vein of a pig weighing 17 pounds, without unduly exciting the animal. The pig was then allowed to drink water after the injection. One half hour later he was killed by a blow in the head followed by bleeding. Anesthesia was not used. Upon examining the viscera, the lower 2 inches of the stomach serosa and the whole of the small intestine were distinctly colored by the dye. The serosa of the terminal 3 feet of ileum was a deep pink color. The remainder of the small bowel showed a lighter pink and the antral portion of the stomach a very light pink. The pancreas and all of the lymph glands were pink in color, more particularly the mesenteric nodes. The salivary glands, trachea, bronchi, lungs, aorta, heart muscles and skin were not stained. Deep red dye was present in the urinary bladder, gall bladder and bile channels. The cut surface of the kidney and liver contained dye. Dye was squeezed out of the ampulla of Vater.

The mucosa of the gastrointestinal tract was exposed. The stomach was stained a deep pink color throughout, distinctly more so proximal to the pylorus for a distance of 1½ inches. There was a sharp line of demarcation, about ½ inch below the cardia, where the pink staining of the mucosa began. Free dye was present, mixed with a small quantity of food in the stomach. The mucosa of the whole of the small intestine was pink, but to a lesser extent than that of the stomach. From a distinct pink the color merged into a yellowish pink below the ampulla for some distance, due undoubtedly to bile admixture. The staining of the mucosa stopped sharply at the ileocecal valve, the colon not being stained. Since the terminal ileum was much more distinctly stained than the upper part of the small intestine, it would appear that the staining was due to excretion by the cells and not to the presence of bile in the bowel.

These experiments justify the following conclusions.

1. Neutral red, when injected intravenously, is eliminated by the entire stomach mucosa and the whole of the small bowel to the ileocecal junction.
2. It is also eliminated in the bile and urine in much larger quantities than in the stomach.
3. It is not secreted in the saliva.
4. The lymphatic structures take it up quickly and the lymph-nodes become colored distinctly with the dye.
5. The whole glandulature of the stomach is active in the secretion of the dye although the antral portion is consistently deeper in color.
6. Animal experiments confirm the impression derived from clinical observation that the bulk of dye injected is not eliminated by the stomach.

The value of neutral red as a test for gastric secretion is largely confined to the diagnosis of achylia gastrica. We believe that the ordinary gastric analysis cannot be relied upon in diagnosticating this condition. Several cases recorded were looked upon as cases of true achylia after repeated fractional gastric analyses. These cases, however, gave a secretory response to histamin, and neutral red was eliminated when injected intravenously.

It has been held by Hirbayashi that local lesions of the gastric mucosa produced experimentally can be recognized by this test, but in our experience no such conclusion can be drawn clinically. If our contention is correct that the dye is secreted by the whole glandulature of the stomach, it is unlikely that a circumscribed lesion of the mucosa will reduce the dye excretion sufficiently to cause a local lesion to be suspected. When the amount of dye is reduced, a differentiation between local lesion and hypoacidity cannot be made.

Regurgitation of bile into the stomach interferes with the quantitative estimation of the dye. It is possible to precipitate the bile from the specimen by a method described by two of us,[6] but some of the dye would be lost in the procedure as it is taken up by the filter

paper. For this reason little information can be obtained by this method in cases that have been subjected to gastroenterostomy. We have observed three such instances.

The elimination of neutral red by the stomach, whether injected intramuscularly or into a vein, is very roughly proportionate to the amount of acid secretion. The appearance time of the dye following the intramuscular and the intravenous injection, is somewhat parallel to the concentration of hydrochloric acid in the stomach. The parallelism is not constant, however, and it is only in the markedly reduced acidities that the results are fairly consistent. The quantitative estimation of the amount of dye eliminated over a two hour period is almost equally unreliable. This method, however, following the intravenous injection of the dye, seems to parallel more closely the acid curve than either the appearance time of the dye or the intramuscular quantitative method.

Neutral red or any other dye, injected either into muscles or veins, cannot supplant or be compared with the fractional gastric analysis as a test for gastric function as a whole. Rehfuss describes the latter test as a method of measuring gastric work, that is, both the secretory and the motor function of the stomach, the latter being frequently overlooked by critics of this method. The dye test measures only the secretory activity of the stomach.

Conclusions. 1. Only a small fraction of the amount of neutral red injected either intravenously or intramuscularly, is eliminated by the stomach. The entire glandulature of the stomach participates in this excretion.

2. The greater proportion of the dye is excreted by the liver, kidneys and small intestines.

3. There is a rough relationship between the amount of dye secreted and the time of its appearance and the degree of gastric acidity. In low-acid stomachs delayed secretion rate and diminished quantities are generally found.

4. Neutral red does not appear in the stomach in cases of true achylia gastrica except when carried there by duodenal regurgitation.

5. Neutral red can be looked upon only as an imperfect test for gastric function, since it furnishes no information as to the motor power of the stomach.

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UNUSUAL EOSINOPHILIA WITH SPLENOMEGALY (EOSINOPHILIC LEUKEMIA?) IN A CHILD AGED SIX YEARS.

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The extreme rarity of this condition makes it desirable to report even single cases and compare them with the few already in the literature.

Case Report. R. Z. was first seen by me, February 16, 1924, at the age of six years. She was referred by a laryngologist because her general health seemed poor.

Previous History. She was the older of two children. Her family history was negative. Birth was normal. She was breast fed for nine months, and for three years following this had difficulty with feeding, with a tendency to diarrheal stools. She also suffered from infantile eczema. At the age of one year she had an attack of influenza complicated by bronchopneumonia. Following this she had frequent attacks of bronchitis and "head colds." At the age of two years her tonsils and adenoids were removed. However, the colds continued, and she had severe attacks of otitis media. Because of a continual running nose, a second tonsil and adenoid operation was performed one year ago.

Present Illness. For the past few months the child had been under treatment by a laryngologist for continued colds and nasal discharge. A pansinusitis had been demonstrated, and a vaccine composed of Staphylococcus aureus, pneumococcus Type IV and hemolytic streptococcus was administered, the patient having had nine injections during the past four weeks. The general condition seemed only slightly improved, and the nose continued running. The child's appetite was fair, bowels regular, she slept well, was bright and wide awake, but had a tendency to irritability. She did not have fever. Operation on the sinus was being considered, but the child's poor resistance and general lack of stamina prompted the surgeon to have a more complete physical examination made.

Physical Examination. This showed a child with a somewhat scrofulous habitus. Her weight was 40 pounds (average for age, $43\frac{1}{2}$), and height $42\frac{5}{8}$ inches (average for age, $43\frac{1}{2}$). Her general condition was good. The skin was distinctly pale, but showed no eruptions. The lips were thick; the nose showed mucopurulent discharge. The cervical lymph nodes were slightly enlarged. The teeth were excellent. Throat examination showed complete removal of tonsils. The chest revealed signs of old rickets, but the heart and lungs were normal. The abdomen was slightly prominent and the spleen was felt two fingers' breadth below the free border, freely movable and very hard. Liver felt three fingers' breadth

below the free border. The urine showed no sugar, albumin or indican. The von Pirquet test was negative. The Wassermann reaction was negative. The blood findings are given in table. As a result of these findings the stools were carefully searched for parasites, stools being sent to three different examiners. All examinations failed to reveal ova or parasites.

On March 20 the child was again seen and the history was carefully searched for a possible attack of trichinosis. The child had had no illness remotely resembling this. Close questioning showed that the spleen had been found much enlarged by Dr. L. E. Holt when the child was two years of age. No blood examinations had been made.

A blood smear on March 20, 1924, showed the results given in table.

On April 6 a complete blood examination by Dr. Nathan Rosenthal showed the results in table.

The child was given 3 drops of Fowler's solution three times a day.

On April 26 she had distinctly larger lymph nodes in the neck, a few small palpable nodes in the axilla and the groin. The spleen and liver were unchanged. For the blood count on this day see table.

One month later the child came to the office on account of a cough which seemed suspicious of pertussis. On June 2, which was the last time I saw the child, she was seen in a definite attack of whooping cough. She was taken home and grew rapidly worse developing a bronchopneumonia with very marked cardiac failure which caused her death within a few days. No further blood examinations were made and no postmortem examination was performed.

Discussion. This case is noteworthy because of the very unusual blood findings: During the two and a half months that the child was under my observation the white blood cells varied from 14,800 to 25,600, the eosinophilic polynuclear cells varied between 37 and 64 per cent and eosinophilic myelocytes varied from 2 to 6.3 per cent. With this blood picture there was associated an enlarged spleen, enlarged liver and a slight general adenopathy. There was practically no anemia.

This syndrome is one of great rarity; I have been unable to find a report of any similar case occurring in a child, though four cases somewhat resembling this one have been reported in adults.

Under the title of "Persistent Eosinophilia with Hyperleukocytosis and Splenomegaly," H. Z. Giffin reports from the Mayo Clinic the case of a male, aged thirty-one years, first examined, March 11, 1913. He gave a history of some febrile illness eight years previously, since which time his health had been poor. For about a year he had suffered from pain in the left thorax and had had

attacks of edema which became generalized and severe one week before admission. Examination showed a marked generalized edema, ascites, spleen extending to the level of the iliac spine and moderate enlargement of axillary nodes. There was no nephritis. The blood Wassermann test was negative. The blood count is shown in table.

An excised lymph node showed a moderate inflammatory reaction: A marked endothelial hyperplasia was present; eosinophilic polymorphonuclear leukocytes were numerous and a few myelocytes were seen.

The patient improved somewhat, but as the splenomegaly and the anemia persisted a splenectomy was performed in 1914. Following this the general condition improved, but the white blood cell count rose to 97,000 and three years later to 211,000, the eosinophil cells varying from 75 to 90 per cent. The patient in 1918 developed pneumonia and empyema, from which he died. The spleen weighed 2110 gm. and had the macroscopical appearance seen in myelogenous leukemia. The spleen, the bone marrow and the lymph nodes showed great numbers of polynuclear eosinophil cells and few myelocytes.

In 1919 Louis Shapiro described a case under the title "Eosinophilic (Polymorphonuclear) Leukemia." The patient, a man aged forty-eight years, was under observation about a year, during which time he showed a splenomegaly, enlarged liver, glycosuria, slightly enlarged inguinal and epitrochlear lymph nodes. The Wassermann test was positive. His blood picture is shown in table.

The autopsy revealed spleen weighing 1268 gm., fatty liver, thrombus in the right heart ventricle. The bone marrow consisted of a mass of cells, eosinophilic myelocytes with myeloblasts predominating, there being no fat spaces whatever. Microscopically the spleen showed thrombosis of vessels with infarcts; Malpighian bodies were diminished; there was infiltration with eosinophilic leukocytes.

R. G. Stillman presented a man before the New York Academy of Medicine in 1912. The patient, aged twenty-seven years, complained of loss of weight and color and showed a general adenopathy and large liver and spleen. The blood picture is given in table.

The patient's later history could not be followed.

In an article headed "Existe-t-il une leucémie a eosinophiles?" Aubertin and Giroux report the case of an adult with chronic cardiac disease. The blood picture is given in table.

There was slight enlargement of the spleen and no increase in the size of the lymph nodes. The case was followed for many years, the blood findings remaining about the same. The case came to autopsy but no detailed findings are given.

BLOOD PICTURES IN EOSINOPHILIC LEUKEMIA(?)

Case.	Hemoglobin, per cent.	Red blood cells in millions.	Leukocytes in thousands.	Per cent.						Remarks.
				Polymorphonuclears.	Small lymphocytes.	Large lymphocytes.	Mononuclears.	Eosinophils.	Eos. myelocytes.	
My patient:										
Feb. 16, 1924	80	..	..	32	24	..	3	41		
Mar. 20	..	..	..	29	16	10	6	37	2	
Apr. 6	80	4.83	25.6	18.3	9.6		1.3	64	6.3	Platelets, 310,000 (Dr. Rosenthal)
Apr. 26	..	..	14.8	17	..	..	0.5	52	5	Basophils, 0.5 per cent.
Giffin's case	69	3.62	15.4	13	18.3	1	..	66.3	..	Basophils, 1.3 per cent.
Shapiro's case	87	4.74	17.9–236	4–32.5	1–13	1–4.5	1–4.5	48.5–86.5	3.5–6.6	Basophils, 5 to 1.3 per cent; basophilic myelocytes, 1 per cent
Stillman's case	..	..	111–165	3.8	4.2	..	0.8	69.8	1.8	Mesoblasts, 0.2 per cent; Eosinophil metamylocytes, 19.4 per cent.
Aubertin's and Giroux's case	..	..	10–26	19.75	3	1.25	11.25	65.75	0.75	

All of these cases show in common a chronic illness accompanied by enlargement of the liver and spleen, increase in the total number of white blood cells, varying from 10,000 to 236,000, and an increase in the eosinophilic polynuclear cells up to 86 per cent. In all of these cases moreover the ordinary conditions giving rise to eosinophilia can be excluded (parasites, skin disease, trichinosis, anaphylactic phenomena, asthma, and so forth). What is the status of these cases? Should they be classed as a form of leukemia or not? In favor of their belonging to this group of diseases is the persistent increase in the number of white blood cells, the increase in the size of the spleen, the enlargement of lymph nodes, the presence of myelocytes in the blood and in some of the tissues examined. Against their being considered leukemia is: (1) The very small number of immature cells in the circulating blood (in my case 6.3 per cent) and (2) the absence of severe anemia. This last fact certainly differentiates these cases sharply from the ordinary leukemias, as for example in Shapiro's case, where even when the white cells reached enormous numbers, the hemoglobin and the red blood cells were approximately normal. The absence of any hemorrhagic phenomena in these cases is also noteworthy.

In Giffin's case the highest total white count before splenectomy was 21,800, whereas three years after the operation counts as high as 211,000 were obtained, and this author is inclined to view this increase as a result of the splenectomy. However, in Shapiro's case the total count rose from 17,900 to 236,000 during the course

of a year without any operative interference whatever. In my case the highest recorded white blood cell count was 25,600, obtained while the child was afebrile and suffering only from a chronic sinusitis. In the light of the other cases the sinusitis would seem to have been secondary and to have persisted in spite of treatment because the child's constitution was undermined by the blood disease. It also seems likely that the child's rapid succumbing to the terminal pulmonary infection may be explained on the same basis.

Whether this case and the other cases described should be classed as leukemia or not remains a matter for argument. The important fact is this: There exists a definite clinical syndrome characterized by a chronic course with splenomegaly, great eosinophilia, persistent leukocytosis at times reaching leukemic proportions and relatively slight anemia. Such a clinical picture may moreover occur in childhood.

Summary. A unique case of extreme eosinophilia is described occurring in a girl, aged six years. During the two and a half months in which the child was under observation she showed a moderately enlarged spleen, slight general adenopathy, leukocytosis varying between 14,800 and 25,600, eosinophilic polymorphonuclear cells varying between 37 and 64 per cent and eosinophilic myelocytes present up to 6.3 per cent.

Four somewhat similar cases in adults are reported from the literature, two with autopsy.

The relation of this condition to leukemia is discussed.

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INCREASED PERMEABILITY OF VESSEL WALLS AS A FREQUENT CAUSE OF PULMONARY HEMORRHAGE.*

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Blood spitting is a frequent symptom of pulmonary disease, particularly pulmonary tuberculosis. A very large majority of all

* Read by title at the Forty-second Annual Meeting of the American Climatological and Clinical Association, Washington, D. C., May 5 and 6, 1925.

patients suffering from active pulmonary tuberculosis expectorate blood sometime during their illness.

It was formerly generally accepted that blood in the sputum meant a destruction of a portion of the wall of a pulmonary vessel, the variation in size of hemorrhages depending upon the size of the vessel in which the opening occurred.

More careful observation of tuberculous patients, however, shows that blood coming from the lungs does not always indicate the same underlying condition. Ulceration of the walls of vessels of some considerable size and rupture of aneurysmal dilatations in cavities occur now and then and cause severe or even fatal hemorrhages. Injury to the walls of tiny capillaries is also a frequent cause of bleeding; but the great majority of pulmonary hemorrhages which occur, evidently from their very nature, are not due to either of these causes. They usually occur and recur under certain conditions, the most common of which are changes in weather, the presence of acute respiratory infections and during the menstrual cycle. They are usually small in amount, consisting of only one or two mouthfuls, but sometimes they are more copious. They frequently persist over several days and are apt to recur when the same or similar conditions again arise. Many of them occur in the early morning hours.

A tendency for tuberculous patients to spit blood during the menstrual period has long been recognized. It has been spoken of as a vicarious menstruation. This, we now know, to be an incorrect explanation. This blood spitting is a part of the general increase in severity of symptoms which occurs at this time, and is undoubtedly due to increased pathologic activity in the tuberculous foci. In explaining this according to the theory of Jobling and Peterson,[1] we assume that prior to the time that the menstrual disturbance occurs the enzymes which are instrumental in breaking down the tuberculous tissue are bound by antienzymes. These latter are not specific. When the enzymes which accompany the menstrual cycle enter the blood stream then a portion of the antienzymes which are binding the former leave them and bind those which accompany menstruation. The former, released, cause increased activity in the tuberculous areas. This increased activity at times appears as increased permeability of the capillaries and results in the escape of blood.

Observations made by different observers, the staff of the Phipps Institute,[2] and more recently Walsh[3, 4] and Montgomery[5] have called attention to an apparent relationship between certain hemorrhages and the presence of pneumococci and other organisms causing acute respiratory infection. This is too well established now to be questioned. I have noted it frequently. I have seen two quite severe hemorrhages accompanying tonsillitis, and many accompany the common acute respiratory infections. The writer[6]

previously stated in describing this type of hemorrhage: "I look upon this type as being due to a congestion much the same as we see in pneumonia and heart lesions. Is it not possible, however, that it might be due to toxic action?" And later:[7] "The theory of toxic action seems to me to be the one which offers the best explanation. Such types of hemorrhage rarely occur except where the disease is active. It is not at all improbable that the hemorrhage is part of a collateral inflammatory exudation."

Browning[8] made a study of symptoms including hemorrhage in its relationship to changes in weather at the Pottenger Sanatorium, and he concluded that there was a definite relationship between their occurrence and barometric changes. Hemorrhages of all kinds are affected by weather conditions. Sudden marked changes from wet to dry, or from dry to wet, fog, sudden hot or cold spells are accompanied by an increase in incidence of blood spitting, which can be readily observed in institutions where a tuberculous population of 100 or more exists.

Recent advances in biophysics and studies on the physiology of the circulatory system suggests a rational explanation for some of the types of bleeding here discussed. Krogh[9] has discussed the effect of capillary poisons which cause such a dilatation of the vessel walls as to permit of ready passage of the constituents of the blood into the tissues. Among substances classed as capillary poisons he mentions certain salts of gold and arsenic, histamin and sepsin. Doubtless there are many substances having such action. Clinical evidence shows that many acute respiratory infections are accompanied by blood spitting. The type of acute respiratory infections which have been common since the pandemic of influenza in 1918 have not only been the cause of blood spitting in many frankly tuberculous patients, but in some in whom I could find no evidence of active tuberculous disease. Either the poisons from the tubercle bacilli or the tuberculous process or that from the germs causing the acute infection could probably act as direct capillary poisons, or there could be an increased permeability of the vessel walls as a result of the increased activity of the local cells. The increased local activity in this type may also be accounted for by the same enzyme-antienzyme action as mentioned in connection with menstruation.

Increased activity is accompanied by an increased permeability of tissues (Lilly[10, 11] and Mathews[12]), so it is quite easy to understand how infections and menstruation, by causing selective action upon the already diseased areas, may have a tendency to cause increased activity in the areas of infection. Cells which are injured are more sensitive than normal cells, consequently an amount of stimulation which is not sufficient to affect normal cells might easily produce effects in cells which previously have been sensitized

by disease so as to cause such a degree of increased permeability as to allow the escape of blood or sanguineous fluid.

It is more difficult to explain the manner in which the blood spitting which accompanies changes in weather is produced. This inability to explain on our part is doubtless partly due to our ignorance of the effects upon the body caused by changes in weather and partly to a failure to appreciate the degree of physiologic adaptation which is required on the part of the body to preserve equilibrium during such changes, and especially to a failure to appreciate the handicap to adaptation which is experienced by those cells which are the seat of disease.

Think of the change that must be effected to cool the air from 120°, 200° and 300°, as is found in heated ovens, to 98.6°, the normal temperature of the body; or to warm it from zero or a − 20° or 40° to that of the normal 98.6° of the body; or of saturating an air with moisture when its relative humidity is reduced to a minimum; or of the adjustment of the body that is necessary for it to function normally in both bright sunshine and in the presence of cloud. Think of the difference in stimulation that attends these various conditions, and the effects produced upon the vessels of the respiratory passages as a result of them.

The influence of the varying content in light rays and in electric units under conditions of storm and pleasant weather, and the changes in barometric pressure under the same conditions, are immense factors in disturbing physiologic action. The normal 14.7 pounds of pressure per square inch of body surface which is found at sea level changes enormously at these times. Huntington[13] says the increase of 1 inch in barometric pressure is equivalent to adding a weight of 1,000,000 tons to each square mile of the earth's crust. This same relative change in pressure is experienced by the human body and means an additional ton of pressure. A decrease in barometric pressure removes weight in the same proportion. These changes call for enormous adjustment. Think what they mean to the superficial body structures and to mucous membranes.

Increased permeability shows itself most frequently in the bronchial mucous membranes, but it is also frequently noticed in the nasal mucous membrane when no apparent inflammatory condition is present.

The type of hemorrhages which depends on these weather changes is most apt to occur at the time of day when atmospheric pressure is low. There are two maximum and two minimum periods of atmospheric pressure each day, and it is interesting to note that the lowest pressure is found in the early morning (about 4 A.M.) hours, and that this is the time when most hemorrhages of this type occur. The second minimum occurs in the afternoon (about

4 P.M.), and this is another time in the day when hemorrhages occur.

According to biophysics, activity in body cells is an electric phenomenon brought about by a difference in potential between the two sides of the cell membrane. The point of injury or the point of stimulation of the cell assumes a negative charge, thus affording the condition necessary for starting an electric reaction. Increased electric reaction, increased cellular activity and increased tissue permeability are concomitant states which accompany action and reaction of tissues.

Summary. Acute infections of the lung are apt to produce their greatest effect at the point where the tissues are now or have been injured by tuberculous disease. This causes increased activity and permeability of tissues, including bloodvessels, which at times result in conditions which permit the passage of blood through the vessel walls.

The menstrual enzyme in some manner causes increased activity in local tuberculous processes, which is accompanied by increased permeability.

Certain weather changes, the exact factors in which we do not know, affect all tissues of the body, but particularly those of the lung which have been injured as a result of active disease, and cause the blood to pass through the capillaries. This is particularly true of those injured by tuberculous infection.

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OBSERVATIONS ON NONPOSTCICATRICIAL KELOID.

With a Report of a Case.

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Literature records but very few exhaustively described cases of keloid (Geyer,[1] McKee,[2] Heidingsfeld,[3] Freund[4]) that did not arise from a previously existing scar. The following case will prove of special interest, since the skin lesion was preceded by purpura.

Case Report. A. F., a white boy, aged four years, admitted to the Out-patient Department of the Children's Hospital on August 5, 1924, was complaining of a peculiar skin rash which appeared about six weeks previously to admission, following chickenpox. New lesions were still in the stage of development.

Family History. His two brothers were perfectly well. There was no history of asthma, eczema, tuberculosis, hyperthyroidism, lues, or hemophilia in the family.

Past History. The child was always in good health. He had had no diseases except measles, in March, 1923. On March 14, 1924, he was taken ill suddenly, the chief symptoms being fever (101°), sore throat and subcutaneous hemorrhages. He was admitted to the Children's Hospital with the diagnosis of purpura.

From the reports at that time the following facts are noted: A well-nourished boy. Temperature, 100.2°; pulse, 104; respirations, 23. On the right side of the forehead is a subcutaneous hemorrhage, the size of a silver dollar, with similar lesions on the right chest, under the right arm, over the abdomen and on the back. The tonsils are enlarged and cryptic. The heart, lungs and abdomen are negative; liver is not enlarged; the spleen not felt. There are no other evidence of hemorrhages (gums, urine, stool).

Laboratory data at that time included a blood count: Red blood cells, 3,743,000; leukocytes, 18,500; hemoglobin, 70 per cent; polymorphonuclears, 77 per cent; lymphocytes: small, 16 per cent; large, 7 per cent; platelets, 240,000; coagulation time, five minutes. Culture of throat, negative. von Pirquet and Wassermann tests, negative. Calcium content of blood, 8.9 per 100 cc. The urine showed no sugar, albumin or casts. During the time he was in the hospital symptomatic treatment was given, and tonsillectomy was performed on March 27. On March 31, when the patient was discharged, the fever had subsided and the hemorrhages were fading.

The patient felt perfectly well except for occasional pains which were described as colic-like, localized in the lower abdomen without association with bowel movement and food ingestion. They generally occurred during the night, and were not relieved by food. There was no abnormality of stool, no icterus, no nausea nor vomiting.

In the latter part of June the patient had chickenpox. The pustules appeared most thickly over the right and left thigh. While the typical lesions of chickenpox were disappearing there developed around them reddened areas from which scar-like elevations arose as seen on the day of admission. The patient came to the hospital for relief from mosquito bites from which he suffered three days previously.

Physical Findings. Temperature, 99.2°; pulse (rectal), 94; respirations, 20. Marked pallor of skin and mucous membranes; no signs of rickets. Eyes, ears, nose, sinuses, teeth and tongue are normal. The tonsillar areas show no diseased tissue left after tonsillectomy. Only the submaxillary glands show some enlargement but they are not tender. The thyroid is not felt. The heart and lungs are normal. The pulse is regular, full and of normal tension and volume. Blood pressure: systolic, 118; diastolic, 86. The abdomen, liver, spleen, genitalia and extremities are negative. The reflexes are normal.

Description of Cutaneous Lesions. 1. Over the right scapula there is a nevus pigmentosus of dark-brown color, the size of a dollar. (Fig. 1 A.)

2. There are a few blue and yellow maculæ on the back and stomach region which have the appearance of former hemorrhages. They are not hyperesthetic and do not show any involvement of the epidermis. (Fig. 1 C.)

3. On the exposed parts of the body, over both arms and legs, on neck and on the face are some inflamed areas from the center of which is a discharge of some serous fluid, such as seen in mosquito bites of two to three days' duration. They show a slow tendency to healing. On the right foot, around one of these areas, there is superficial edema of unusually large size. It extends from the middle of the foot over the ankles.

4. On the outside of both legs are peculiar lesions which at first inspection remind one of urticaria. There are numerous erythematous areas varying in size from that of a pea to that of a man's palm. They are not elevated, of violet-rose color and do not disappear on glass pressure. Their outline is not definite. There is no defect of the epidermis. Out of the largest areas scar-like formations arise, somewhat paler than the patient's skin, white on pressure and about 2 to 3 mm. elevated over the level of the skin. These scars are of a striking shape and different in all lesions. On the erythematous patch of the right upper leg the scar forms one

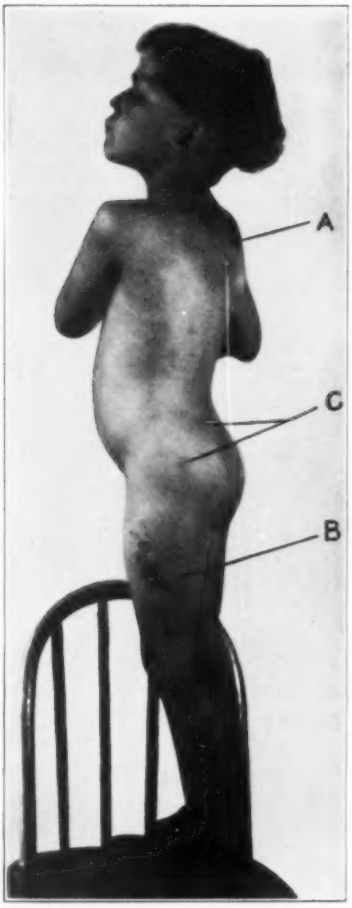

FIG. 1.—Photograph showing A, nevus; B, keloids; C, hyperpigmentations, residues of purpura.

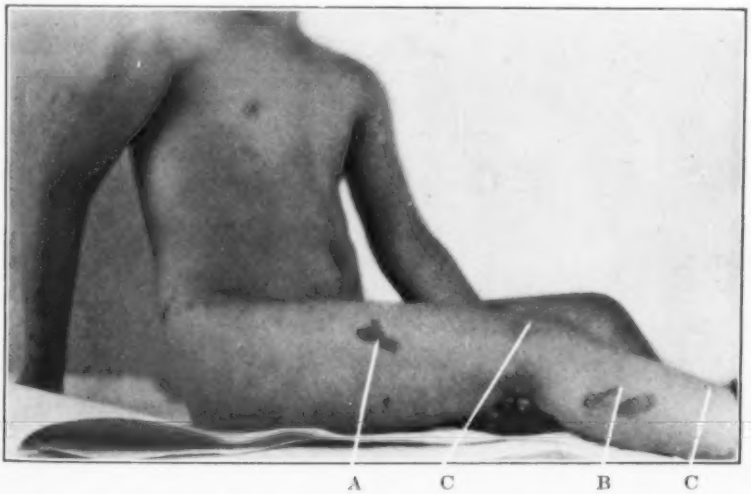

FIG. 2.—Keloids on right leg. A, showing transverse bifurcations; B, circular form; C, beginning growth.

FIG. 3.—A, fully developed keloids; B, rudimentary papule-like forms.

FIG. 4.—Linear scars surrounded by hyperpigmentated areas. Residues of purpura on left leg.

straight line, about 4 cm. long, giving off three branches on both ends and in the middle, of about ½ cm. each (Fig. 2 A). On the manifestation of the right lower leg it is more circular and horseshoe-like (Fig. 2 B). On all the lesions we find similar, more or less marked branches coming out from the chief line. On the smaller erythematous areas the scar formations are of rudimentary form, in the smallest areas being like papules (Fig. 3 B). The scar does not extend deeply into the skin, nor does it adhere to the subcutaneous tissue. They cause slight itching and, what the child describes as a pulling sensation.

Laboratory Findings: Blood: Leukocytes, 9900; hemoglobin, 80 per cent; red blood cells, 4,060,000; polymorphonuclears, 58 per cent; large lymphocytes, 7 per cent; small lymphocytes, 20 per cent; eosinophils, 14 per cent; basophils, 1 per cent; coagulation time, six minutes twenty seconds. Red cell fragility: Partial hemolysis at 0.35 per cent; complete at 0.2 per cent. The routine urine examination is negative, also for urobilin, urobilinogen and bilirubin. The stool shows no ova or parasites.

Course of Disease. August 8, 1924: The patient is being treated with fibrolysin injections (Merck), 1 ampule (1 cc) every third day. For the abdominal pain tinctura belladonnæ is being given. In addition, as a local application, pepsin hydrochlorid is used over two of the lesions (Unna,[5] Wassermann[6] and Friboes[7]).

September 2, 1924: The abdominal pains have disappeared. The erythema around the scars is fading. The scars, however, are still well marked but smaller in size; for instance, on the right upper leg 2 cm. long (against 4 cm. before). Most of the branches have completely gone. The eighth injection of fibrolysin is given. Pepsin hydrochlorid has been discontinued, since no difference in the appearance between the locally treated lesions and the untreated ones could be seen.

October 2, 1924: The child has had several bruises from fall on both legs which healed completely without formation of a scar. Fibrolysin has been discontinued after the fifteenth injection.

October 14, 1924: The von Pirquet test was done over the nevus, experimenti causa, in order to set a stimulus for a new scar. Blood count: Eosinophils, 8 per cent.

October 18, 1924: On the place of the von Pirquet scarification inside of the nevus two small depigmented areas are present. No scar or epidermal defect. von Pirquet was negative.

April 3, 1925: Examination of the child with special attention to skin was completely negative.

Comment. In summing up these data we have a case of keloid in a child who suffered a few months previously of acute purpura, of which residue was still visible. Some of the keloid lesions were observed while developing. The diagnosis keloid is definite, since

we have typical scar formation with the characteristic branches (Kele means "Claws of a Crayfish," Alibert[8]). In view of the well-developed scars no other dermatologic condition is to be considered in differential diagnosis. The purpura is apparently of the Henoch type, being associated with and followed by abdominal pains. The platelet count of 240,000 also points to the diagnosis of Henoch's disease, in which condition the platelets are usually not markedly diminished, but are normal or even increased (Lucas and Fleischner[9]). The purpura improved after tonsillectomy. The eosinophilia is to be noted while the skin eruption was present. An attempt to elicit keloid lesions artificially failed.

Mention is to be made of the increase in resistance of red cells to hypotonic salt solution, although the total count was normal. As animal experiments of Musser and Krumbhaar disclose, there is a decrease of the red cell resistance in artificial purpura.[10] Should our observation indicate that during convalescence from purpura the resistance of the red cell increases possibly as a sign of the regenerative power of the organism? Unfortunately no further blood studies have been carried out.

On March 28, 1925, checking of the fragility showed: Hemolysis, partial at 0.35 per cent; total at 0.25 per cent; hemoglobin, 75 per cent; red blood cells, 3,720,000.

For treatment we intended to apply the most valuable measures —roentgen ray (Cumberbatch,[11] Pfahler[12] and Fox[13]), or radium (Daland,[14] Harrison[15]) in case of failure of the fibrolysin treatment, which has been recommended by Gougerot.[16] After fifteen injections of fibrolysin, however, the skin lesions disappeared completely and therefore the application of roentgen ray was unnecessary. Eight months after the treatment had been started the skin still appeared perfectly normal.

Discussion. The description of this case calls forth the following questions:

1. Does there exist a spontaneous protopathic keloid which arises on an apparently normal skin?

2. Is it possible that the hemorrhagic disease caused a disposition of the skin for keloid?

3. Are there any conclusions as to the pathogenesis of keloid suggested through the observation of the above described case?

Since Alibert's[8] observation first has led to distinguishing two kinds of keloid, that is, one which develops from a skin area not the seat of a manifest injury and the ordinary keloid growing from a cicatricial change of the skin, there has been much discussion in the literature as to whether such a differentiation is justified. Warren, Kaposi[17] and others tried to demonstrate histologic changes to uphold this division. Halbe, Hutchinson, Freund, Unna and, in recent years Heidingsfeld, disprove their arguments, and believe that careful histologic research brings to light features in both

groups which have been thought typical for either one of them. It seems to me that there are two factors which account for the divergence of opinion: (1) Many of the reported cases grouped under the diagnosis keloid are definitely something else, for example, molluscum fibrosum, neurofibroma, myofibroma, verrucca, lacking the characteristic bifurcated prolongations and the typical crests as postulated by Alibert; (2) the meaning of the words "true," "idiopathic" or "spontaneous" keloid is interpreted by different authors in different ways. Some use this term if the history fails to reveal a formerly existing scar (from an operation, burn and so forth). Some others apply it in another sense, referring to a preceding traumatism. It is evident that a classification on the latter basis cannot be upheld, since the occurrence of a trauma is as difficult to prove as to disprove. On the other hand, there are some cases of definite nonpostcicatricial keloids described, for example, by Geyser,[1] McKee[2] and Heidingsfeld.[3] The above case, in which some of the keloids were developing under our observation from skin lesions, which usually do not heal with scar formation, such as purpura hemorrhages and chickenpox, lends support to the old distinction of Alibert, at least from a clinical standpoint.

On careful search of the literature no case records could be found presenting an association of purpura with keloid. However, Minot and Lee[18] do mention residue of purpura characterized by "elevation and induration beneath the skin, leaving a single bluish area usually 2 to 6 cm. in diameter, often with a raised lump in the central part." From this description one has to infer that these lesions are identical with the above described ones, with keloid.

The question arises: Might purpura be the cause of the keloid or at least have created a disposition of the skin to answer such a stimulus as mosquito bite or chickenpox papules by the peculiar production of keloid? This leads us to review the former theories on the pathogenesis of keloid. Most authors believe in a "general disposition" of the individual for keloid, usually not committing themselves in regard to the nature of this disposition. Alibert, Hebra and Hutchinson emphasize the hereditary factor. Justus[19] concludes from the observation of 45 secondary keloid cases associated with some symptoms of hyperthyroidism that the glands of internal secretion, especially the thyroid, play a great part in the origin of this "keloid-disposition." He has even succeeded in producing keloid artificially in 12 of 15 hyperthyroid cases by such irritation of the skin as mustard plaster and carbon dioxide snow. Among the authors who deny the question of a general disposition, believing in a local agent on the seat of the keloid, are Balzar and Levy.[20] De Beurman and Gougerot[21] hold that the tubercle bacillus can produce the lesion. Hyde[22] publishes his observation on guinea pigs, which developed tuberculosis after injection of cell tissue excised from keloids.

In our dermatologic description we noticed that there was some residue of the former hemorrhages left in the form of some pigmented patches. It is well known that keloid is observed chiefly in negroes, in whom we see a natural hyperpigmentation. Furthermore, displacement of pigment has been found as being associated with keloid by former investigators. Welander[23] tatooed a white man with certain dyes. With some he produced keloid, whereas other ones, like the ordinary blue tatoo dye, were without any effect on the skin. In addition, there is no doubt that the production of all scars goes hand in hand with a certain displacement of the skin pigment. We, therefore, have enough evidence to justify the opinion that in our case the change in the pigment distribution, brought about by purpura, may account for the existence of keloid. Moreover, we recall that the child had a large nevus pigmentation over the scapular region. Although we were unable to produce keloid over this area by scarification, I wish to make mention of the possible relationship of this nevus to the genesis of the keloid. Also the other peculiarities of the patient's skin, such as the slow tendency of the mosquito bites to heal and the marked edema of the foot around the mosquito bite lesion, should be mentioned.

With this in mind, especially considering that all scars are associated with displacement of pigment, we see that the question of idiopathic or false keloid assumes another aspect. Instead of the old debate, is there a scar or no scar as a preëxisting causative agent, it might be useful for further investigators to inquire whether there is a change of the pigment distribution as the underlying cause for the keloid, either in the presence or the absence of a scar. This consideration would naturally not lead us much nearer to the solution of the keloid problem, but it might be a step forward on the difficult path leading into the still unexplored large provinces of the pathology of the tumor and of the pigmentation.

Summary. 1. A case of multiple keloid is described which did not arise from a preëxisting scar. Some of the lesions developed under observation.

2. There were definite changes of the pigment distribution of the skin following Henoch's purpura, from which the child had suffered five months previously. There was also a nevus pigmentosus present. The skin had a tendency to heal slowly after mosquito bites.

3. The patient's blood picture showed definite eosinophilia while the keloid was present.

4. The lesion healed after fibrolysin injections. Pepsin hydrochlorid compresses, locally applied, were of no evident value.

5. The opinion is expressed that the presence of pigment disturbances of the skin might be a useful guide in further studies of the Keloid problem, and might help to eliminate further controversy on the question of idiopathic and secondary keloid, in view of the fact

that all scars cause some displacement of the normal pigment conditions of the skin.

(I wish to thank Dr. Udo J. Wile, Ann Arbor, for suggestions given in reviewing this paper.)

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SUBPHRENIC ABSCESS: A CLINICAL STUDY.*

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Localized suppuration beneath and in more or less intimate contact with the diaphragm, usually termed subphrenic or sub-

* Read before the Mount Sinai Hospital Clinical Society, February 24, 1925.

diaphragmatic abscess, offers to the medical man or surgeon a most difficult diagnostic problem. Mistakes are frequent and often justifiable. Insidious in onset, protean in its manifestations, this condition may present a symptomatology so varied and so misleading that definite diagnosis is at times impossible and can only be made with certainty by operation or at autopsy. Let us consider briefly a history such as the following:

Case Reports. CASE I.—Mrs. E. S., a young woman, aged twenty-six years, was admitted to the surgical wards of the Mount Sinai Hospital, December 28, 1922, with the usual signs and symptoms of acute appendicitis. At operation a badly inflamed, almost gangrenous, but not ruptured appendix was removed and the wound closed without drainage. An uneventful postoperative recovery followed and the patient was discharged in twelve days apparently well.

Two months later she was readmitted to the medical wards, complaining that for several days she had been having attacks of chills, fevers and sweats lasting often for two hours and accompanied by vomiting. She complained also of pain in left lower chest and a cough with scanty expectoration. This history together with physical findings of dulness and absent breath sounds at left base suggested a lung or pleural lesion. A roentgen ray of the chest, however, showed no evidence of consolidation or effusion and both diaphragms were normal in position and regular in outline. A negative Widal reaction, sterile blood culture and the presence of leukocytosis seemed to exclude a possible typhoid infection and failure to find malarial parasites in smears ruled out malaria. Because of the septic temperature, the history of a previous appendectomy and the marked tenderness on pressure over the lower chest and splenic area, a tentative diagnosis of abscess of the spleen or subphrenic area, was made. Operation, performed March 24, 1923, revealed a large mass in the left hypochondrium which seemed to be the spleen enlarged to six times its normal size, apparently the seat of multiple infarcts. No subphrenic collection could at this time be made out. Puncture of the spleen with a needle detected no pus and the wound was closed without drainage. The postoperative course was stormy, patient grew progressively worse, temperature increased and, in spite of transfusion, death resulted nine days after operation.

Autopsy revealed a huge subphrenic collection of pus which was situated behind the spleen pushing it forward and thus accounting apparently for the fact that it was not discovered at operation, but simply considered part of a large spleen. The spleen at autopsy was just a trifle larger than normal and contained many degenerated cysts.

In this case in a consideration of its differential diagnosis condi-

tions so seemingly varied as typhoid fever, malaria, pleurisy with effusion, lung abscess and abscess of kidney or spleen had to be ruled out and even then, in spite of roentgen-ray examination and operation, diagnosis could only be made with certainty at autopsy. Similar and more recent cases have served to emphasize the diagnostic difficulties of this condition.

In an effort to bring before our minds a clearer picture of subphrenic abscess a clinical study of some of our cases gathered from our records together with additional facts gleaned from recent literature on this subject seemed worthy of presentation.

Since 1921 only 6 cases have been seen in our medical and surgical wards, indicating how infrequently this condition occurs.

In order to appreciate more clearly the location and causes of these abscesses and from the standpoint of operation in order to determine the best method of approach for drainage, some knowledge of the anatomy of the subphrenic spaces is necessary. Detailed description of these spaces particularly of their divisions into the six areas, as given originally by Barnard,[1] will not be attempted. For practical purposes it is only necessary to remember that the subphrenic spaces lie in the upper portion of the abdominal cavity beneath the under surface of the diaphragm in the so-called supra-colic area and that in this area they are subdivided into the right and left subphrenic spaces by the falciform ligament of the liver. The right subphrenic space is therefore in relationship anatomically above with the right portion of the diaphragm, while below it is in relationship with the liver and posteriorly with the gall bladder, duodenum and upper pole of the right kidney. Abscesses in this space usually originate from lesions of these organs such as abscesses of the liver or kidney; duodenal ulcer of infection of the gall bladder or ducts. The right space connects freely with other fossæ and particularly by way of the right lumbar groove lying between the ascending colon and loin with the appendiceal and pelvic regions. As a consequence appendicitis is a common etiologic factor and most of the abscesses caused by it are right sided, although left-sided abscesses do occur, as in the case already cited.

On the other hand, the left subphrenic space situated beneath the left portion of the diaphragm is in relation with the many organs: the spleen, left lobe of the liver, cardiac end and posterior wall of the stomach, left kidney and adrenal and tail of the pancreas. Lesions of these organs, therefore, may by perforation or extension result in abscesses of this space—often called perigastric or perisplenic and because of the many conditions in this region which they may simulate it is little wonder that the differential diagnosis is so difficult.

It is natural for anatomic reasons that the location of these abscesses should depend in large measure upon the causes and that among the most common of these, appendicitis, ruptured peptic

ulcer and infections of the liver or gall bladder should predominate. Unquestionably gravity plays a great part in the selection of the subphrenic space for localization of the abscesses; thus, if for any reason fluid accumulates in the peritoneal cavity either before or after operation and the patient is not in a sitting posture, this fluid will tend to gravitate to the subphrenic spaces instead of flowing down over the lumbar elevations into the pelvis. Here absorption is not so rapid, abscesses not so prone to develop, and even if they do, they can be more easily dealt with, particularly in the female. It is a peculiar fact in this connection that most subphrenic abscesses occur in males (84 out of 113 in Mayo series).[2] This is no doubt best explained by the fact that anatomic variations between the male and female pelves allow the lumbar grooves to drain more readily into the pelvis of the female than of the male and therefore in the female, pelvis abscess is more commonly the sequel than subphrenic abscess. Extension of intrathoracic suppuration through the diaphragm to cause a subphrenic abscess is indeed a rare occurrence and is best explained by the fact that the current of lymph flow through the diaphragm is ascending and not descending. Focal infection is also mentioned in the literature as an etiologic factor, and though cases have been cited as apparently due to carbuncles, cellulitis or dental infection, this mode of infection is the exception rather than the rule. In most cases, the abscess is due to infection from some abdominal viscus.

Acute appendicitis, particularly the type which is neglected and allowed to go several days or weeks before operation, is far too frequent a cause of subphrenic abscess. In this type one obtains a history similar to the following:

Case II.—M. S., a boy, aged seventeen years, was admitted to the Mount Sinai Hospital August 31, 1921, with pain in the right iliac fossa of three weeks' duration, septic temperature, leukocytosis, marked tenderness and rigidity over the hypochondrium with only slight tenderness over McBurney's point. At first the diagnosis of cholecystitis or high-lying retrocecal appendicitis seemed likely. On account of some vague signs in the lower chest posteriorly, a roentgen ray of the chest was taken and revealed no lung lesions, but did show elevation of the right diaphragm with no irregularity in outline. The diagnosis of subphrenic abscess was then made and verified at operation. The abscess was drained and a large subacutely inflamed appendix removed. After a rather stormy convalescence, lasting over six weeks, the patient left the hospital with a moderate anemia and a small discharging sinus which required considerable time to heal.

In this case an earlier recognition and prompt operation would have prevented the formation of the abscess, shortened materially the convalescence and promoted the well-being of the patient.

More often, however, the abscess forms after the appendectomy has been done. Thus Ross[3] reports an incidence of about 0.8 per cent in a series of over 3300 appendectomies at the Lankenau Clinic. It is more apt to occur in a highly placed, retrocecal, gangrenous appendix, where ascending retroperitoneal infection is already present at the time of operation. This method of spread of infection (namely, through the retroperitoneal cellular tissue) is the most common. Infection can, however, be carried through the lymph channels or rarely through the portal or general circulation. In this type of case, the symptoms appear several days after operation, as in the following case:

CASE III.—A. L., a man, aged twenty-five years, was admitted to the Mount Sinai Hospital, September 3, 1921, complaining of pain in the lower right abdomen and vomiting for five days with a history of similar previous attacks. His temperature and pulse were normal, lungs presented no abnormal signs, and there was but slight tenderness and rigidity at McBurney's point, with only a slight leukocytosis. At operation, performed the day of admission, an acutely inflamed appendix was removed and the wound closed without drainage. Following the operation, the patient did poorly. He complained of pain in the incision and the right lower chest and back and had a variable but high temperature. A week following the operation considerable pus was evacuated from the incision with but slight relief to the patient. Examination several days later revealed decreased fremitus with dulness and absent breath sounds at the right base and also a leukocytosis of 14,000 with 93 per cent polymorphonuclears. Roentgen-ray examination at this time showed a dense shadow over the lower right pulmonary region with displacement of the heart to the left, suggesting pleural effusion, although a subdiaphragmatic collection could not be excluded. The patient grew steadily worse, began to have chills and looked septic. On October 7, more than a month after the first operation, a longitudinal incision was made into the right loin below the ribs and considerable pus evacuated from a pocket behind the kidneys. Following this operation the patient gradually improved, his temperature gradually returned to normal and after a convalescence lasting over two months, he was finally discharged in good condition January 3, 1922. Roentgen-ray examinations made subsequent to the second operation showed gradual but progressive improvement in the pulmonary involvement with the diaphragm elevated, immobile and slightly irregular in its outer portion, no doubt due to an existing pleuritis.

In this case symptoms of subphrenic involvement began to show themselves four days after operation and continued for almost a month before the abscess pointed in the loin. Of particular interest in this case are the chest symptoms and signs. These are present

in almost every case, and offer one of the greatest obstacles in differential diagnosis. Because of the comparative frequency of postoperative lung complications, especially pneumonia, it is quite natural for any lung signs or symptoms occurring after operation to be mistaken for a pulmonary complication and lead to a delay in the recognition of the true underlying cause. This is well exemplified in Case IV.

CASE IV.—J. D. S., a boy, aged fifteen years, was admitted to the Mount Sinai Hospital April 27, 1923, with the usual symptoms and signs of acute appendicitis of two days' duration. At operation a suppurative appendicitis was found which was removed and drainage inserted. His condition immediately following operation seemed fairly good. At the end of three days his temperature was normal and the wound seemed to be draining fairly well. On the fourth day, however, the patient began to have a slight cough and an expectoration, the temperature increased and on account of the symptoms together with a polymorphonuclear leukocytosis and physical signs at the right base suggestive of consolidation (dulness and tubular breathing) pneumonia was considered. Roentgen-ray examination at this time showed evidence of pleurisy with a slight effusion and an incomplete consolidation involving the lower portions of the right lung. The outlines of the diaphragm were completely obliterated, making it impossible to distinguish between a subdiaphragmatic and a supradiaphragmatic collection (Fig. 1). With improvement in the wound drainage the patient gradually became better, his temperature fell and the cough decreased in intensity. Physical signs at the base persisted for some time, but chest roentgen-rays taken subsequently showed gradual absorption of the effusion and improvement in the lung picture. With absorption of the fluid, the right diaphragm was then seen to be somewhat elevated, indicating that a subdiaphragmatic collection had been present. The patient was discharged June 3, 1923, apparently well, in spite of roentgen-ray evidence of slight basal involvement. Follow-up showed no return of any symptoms during the following year.

In this case the presence of the subphrenic abscess was further complicated by pleurisy with slight effusion and inflammatory involvement of the lower lung, no doubt the result of upward extension of the subphrenic infection through the diaphgram. The complication is a fairly frequent one, and is one of the prime obstacles in making a diagnosis of abscess possible. In this type of case, history is most important, since roentgen-ray findings lend no assistance.

From a review of the cases already cited it can be readily seen that the symptomology is varied and dependent largely upon the

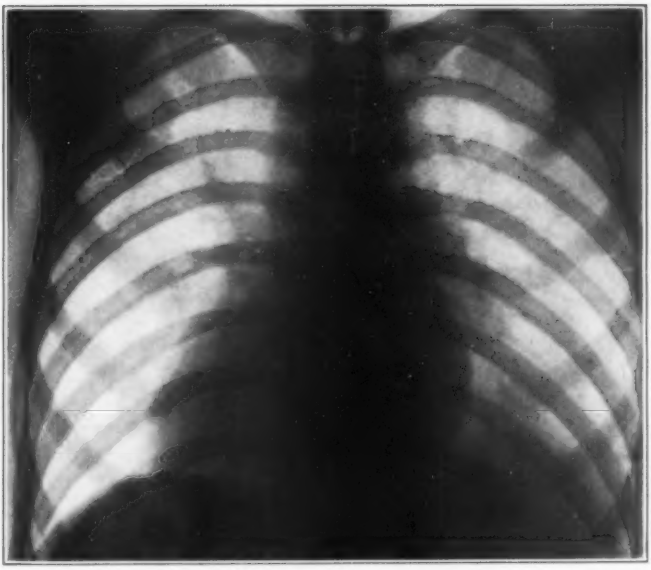

FIG. 1.—Case IV. Chest roentgen ray indicating difficulty of making diagnosis by roentgen ray when subphrenic abscess is complicated by pleural effusion.

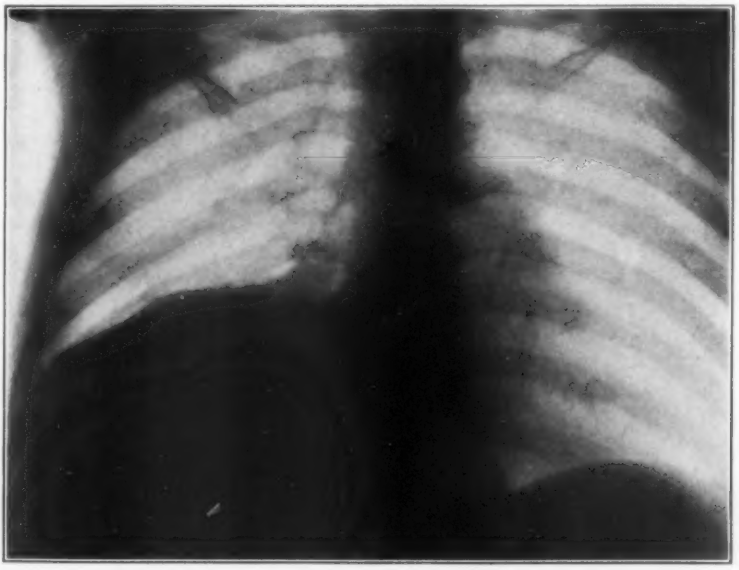

FIG. 2.—Case VI. Chest roentgen ray showing elevation of diaphragm due to subphrenic collection.

etiology, location, and more particularly upon the character of the onset—when acute, as in ruptured ulcer, the onset is usually abrupt with acute abdominal pain and vomiting of either bloody or bilious material followed later by constitutional signs of suppuration, namely, fever, rapid pulse, chills, sweats, pallor and a polynuclear leukocytosis. More often, however, the onset is insidious, and in these types the most constant symptoms are: (1) Pain at the costal margin referred to the back or shoulder. (2) A church-steeple type of temperature curve, that is, one showing marked variations with corresponding increase in the pulse rate, but rarely in the respiratory rate. This lack of correspondence between the respiratory and the temperature-pulse curve, when associated with a chill and leukocytosis is very diagnostic of inflammation about the diaphragm. (3) Leukocytosis. This serves to indicate the presence of suppuration, but not its location. (4) A short diaphragmatic cough present in many cases particularly when there is coexistent pleural involvement. Severe cough with marked expectoration occurs only after rupture of the abscess into the lung.

Physical signs are as variable as the symptoms; in fact, in the early stages no local signs may be found unless carefully looked for. One of the early signs is a limited excursion of the diaphragm on the affected side, also a retraction of the interspaces directly over the abscess. In right-sided abscesses not containing gas, the area of liver dulness is increased and often friction sounds are heard over the dome of the liver, indicating basal intrathoracic involvement. As the abscess gets larger, signs of lung compression begin to appear and the area of liver dulness increases. When this occurs, there is usually bulging of the lower ribs or a mass in the lower abdomen on one side, with deep-seated tenderness on pressure. If the abscess contains air, the diaphragm may be pushed up to the level of the second or third rib, giving physical signs on percussion and auscultation of a pneumothorax particularly the tympanitic resonance and movable dulness—this form has been called pyopneumothorax subphrenicus.

At best, physical signs offer but little assistance in diagnosis, particularly in the early stages. Probably the most valuable single diagnostic aid, aside from history is the roentgen ray and fluoroscope. Use of the latter is often prevented by the patient's condition. It should, however, be used whenever possible, as it gives valuable information hard to elicit by other methods. A dome-like elevation of the diaphragm into the thorax with a limitation of the diaphragmatic excursion on breathing and an acute costophrenic angle in the absence of lung involvement is almost pathognomonic of subphrenic abscess (Fig. 2). Where, however, the abscess is complicated by pleural effusion or empyema on the same side, it is impossible to separate the shadows and diagnosis must be made by other methods (Fig. 1). A point of value in differentiating

abscess from pleural effusion, is the fact that in abscess, the heart is seldom displaced laterally, although it may be pushed up. In gas containing abscesses, a pocket of air lying beneath the diaphragm will show on the plate and if the patient can be fluoroscoped either in a standing or in a lateral position, lying on his unaffected side, then a distinct fluid level, lying below the gas, can be made out.

Exploratory puncture of the posterior chest for diagnosis is somewhat dangerous and should only be used when absolutely necessary or to rule out pleural effusion. It should always be carried out in the operating room where preparation for an immediate incision and drainage has been made, should the abscess be located. In the latter instance, to prevent infection of the pleural cavity, the needle should be left *in situ* and incision made down upon it immediately. A negative puncture does not rule out the possible presence of an abscess.

In the final analysis the diagnosis of subphrenic abscess is dependent on the history, mode of onset, physical signs and roentgen-ray findings, and even in spite of these the abscess is frequently overlooked. It is easy enough to diagnose suppuration in these cases; but to locate its site, is a problem sometimes impossible of solution. At times, in spite of history and other diagnostic aids, the abscess is overlooked entirely and not discovered except at autopsy, as occurred in the following case:

Case V.—Mr. M. N., aged forty-nine years, was admitted to the Mount Sinai Hospital, November 8, 1924, with pain in the right hypochondrium and vomiting but no fever or jaundice. There was a history of frequent attacks of right upper abdominal pain and indigestion for a number of years but the present attack dated back three weeks. Examination showed exquisite tenderness and slight rigidity in upper right abdomen with a distinctly palpable liver edge. The temperature and pulse were normal and there was a leukocytosis of 13,800 with 72 per cent polymorphonuclear. Operation performed the day of admission under local anesthesia revealed an acutely inflamed greatly thickened gall bladder filled with calculi and surrounded with extensive adhesions to the duodenum and transverse colon that were separated with considerable difficulty. A cholecystectomy and appendectomy was done and drainage of the gall bladder fossa was inserted. The wound drained but slightly and after a few days the tube was removed leaving a small sinus from which some pus discharged itself. Except for some discomfort in the right upper abdomen and slight vomiting, the patient appeared to improve, temperature and pulse being at this time normal. Twenty days after operation there was a sudden rise of temperature to 104° with rapid pulse, difficulty in breathing and vomiting. Physical signs at the right base, dulness and distant breath sounds, suggested

a pulmonary complication. In the course of the next few days the temperature dropped, the pulse improved, and the patient appeared on the way to recovery. On December 5, four weeks after operation, the patient suddenly became worse, with feeble pulse; and in spite of stimulation, death ensued. At autopsy the gall bladder fossa was found to be perfectly clear. A large subphrenic abscess was found situated in the anterior portion of the right subphrenic space, which accounted for the patient's death.

It is very probable that the abscess in this case formed postoperatively since symptoms did not show themselves for almost three weeks and as a rule, it takes but two weeks for the abscess fully to form itself. Here again, the pulmonary symptoms and signs aided in overlooking the presence of the abscess. This is not infrequent, however, in the Mayo Series, 27 of the 117 cases reported came to autopsy undiagnosed, and many of these were overlooked at operation.

Though subphrenic abscess may resemble many other conditions, the problem of differential diagnosis, practically resolves itself into distinguishing between hepatic abscess, pleurisy with effusion, particularly empyema. History, physical signs and roentgen-ray findings in these two conditions will usually serve to distinguish them. Thus in pleural effusion, there is often a history of previous pulmonary infection, the heart is shifted laterally, the area of dulness changes with the position of the patient and roentgen ray shows a flattening of the dome of the diaphragm instead of an elevation. In hepatic abscess, particularly the parasitic form, there is often a history of diarrhea, the area of liver dulness is not only enlarged upward but also downward (a thing which is unusual in subphrenic abscess) and finally the diaphragm though elevated in the roentgen-ray plate is usually irregular in outline.

If these conditions were to occur singly, diagnosis would not be difficult but more often they occur together. This is especially true in the case of hepatic abscess which often ruptures into the subphrenic space and thence involves the pleural cavity as occurred in Case VI.

Case VI.—B. G., a boy, aged nineteen years, was first admitted to the Mount Sinai Hospital, December 7, 1923, complaining of pain in the right lower chest, slight fever, occasional attacks of diarrhea and weakness, these symptoms being of about three months' duration. He was born in southern Russia and came to this country only a few months prior to admission. Several weeks previously he had been in another hospital for the same complaints and a diagnosis of pleurisy had been made. Examination showed diminished fremitus and breath sounds with impairment of resonance at the right base and a tentative diagnosis of pleurisy was made.

At the end of three weeks he left the hospital but slightly improved.

After his discharge, the pain recurred and the weakness became so marked, that for two weeks prior to his readmission he had to remain in bed. He was readmitted January 30, 1924, with the same symptoms. Examination at this time showed an increased area of flatness with absent breath sounds at the right base, a distinctly palpable liver edge, temperature of 101° and a slight leukocytosis. Roentgen-ray showed a dense shadow on the right side with elevation of the diaphragm, apparently due to a subphrenic collection (Fig. 2). There was also slight displacement of the heart to the left. On February 2, a resection of the eighth and ninth ribs posteriorly was done, revealing a subphrenic collection arising from a large hepatic abscess. This was incised and drainage tubes inserted. Examination of the pus from the abscess revealed the presence of ameba. The postoperative course was stormy, there was evidence of an increasing pleural effusion and the patient grew progressively worse until the time of his death February 17. Postmortem examination showed a large subphrenic abscess and a plastic pleurisy with moderate effusion. The lower portion of the right lung also showed evidence of inflammatory changes.

This case well illustrates the delay in diagnosis caused by the presence of pleural complications. With earlier diagnosis and prompt treatment a fatal outcome might have been prevented. In reviewing the causes of death of 36 fatal cases in his series, Barnard found that in 24 of these, death was avoidable, in 50 per cent by earlier recognition, and in the other 50 per cent, by better drainage at operation. Without operative measures, the outcome is almost certain to be fatal, death occurring either by septicemia or by rupture into the lung, pericardium, stomach, or less often into the bowel. It is possible for the abscess to burrow into the skin and evacuate itself spontaneously, but this occurrence is exceedingly rare. Even with operative treatment, the prognosis in these cases is not very hopeful, mortality being from 20 to 40 per cent in most of the clinics. It is dependent in large measure upon the cause—thus in abscesses due to ruptured peptic ulcer, it is apt to be higher than in those of appendiceal origin.

The treatment of these abscesses, as with any abscess is strictly surgical, consisting of incision and complete drainage. The method of approach to the abscess is best decided upon by the surgeon and is determined largely by the location of the abscess and condition of the patient. A thorough knowledge of the anatomy of the subphrenic spaces will aid greatly in deciding the type of operation to be done. Three methods of approach are generally used: (1) A lumbar incision—if the abscess points here; (2) abdominal incision; (3) through the chest wall posteriorly. In this method the incision is made either below the pleura or through it. In either case the pleural cavity should be protected from infection before opening

the diaphragm. As a rule the posterior method is the method of choice as it insures more complete drainage. Any method which insures easy access to the abscess and complete drainage will be the best for the patient for it is upon this that the outcome depends. Careful study of autopsy findings in the fatal case of Barnard's series upon which operation had been done showed very distinctly that the death was usually due to incomplete drainage as a result of insufficient exposure of the abscess.

Conclusions. From these observations the following conclusions may be drawn: 1. Subphrenic abscess, though infrequent, is a serious condition and often fatal. Convalescence from it is long, tedious and sometimes attended by a thoracic or renal complication that may make the patient a chronic invalid.

2. The location of the abscess is dependent in large measure upon the cause. In the selection of space, gravity plays a large role. Efforts should therefore be made to prevent this by the use of the Fowler position postoperatively.

3. Subphrenic abscess is always secondary to infection elsewhere; most often from a neighboring abdominal focus.

4. Since the majority occur postoperatively, abscess should be suspected in all patients who for no obvious reason maintain a variable type of temperature-pulse curve.

5. Diagnosis is made chiefly upon the history, mode of onset and physical signs. Roentgen ray and fluoroscopy, particularly the latter, are often invaluable diagnostic aids except in the presence of thoracic complications.

6. The frequent occurrence of thoracic complications adds greatly to the difficulties of differential diagnosis.

7. Needling of the thorax should only be performed when absolutely necessary. It should always be done on the operating table under anesthesia with full preparations for immediate operation.

8. Early diagnosis followed by prompt incision with complete exposure and thorough drainage of the abscess will do much in producing a favorable outcome. A thorough knowledge of the anatomy of the subphrenic spaces is essential in determining the best methods of approach to the abscess.

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REVIEWS.

RHEUMATIC HEART DISEASE. By CAREY F. COOMBS, M.D., F.R.C.P. (LOND.). Pp. 376; 51 illustrations. New York: William Wood & Co., 1924. Price, $4.50.

IN his preface the author points out the fact that rheumatic heart disease has not hitherto been made the subject of a monograph. This deficiency in the literature has here been most completely and satisfactorily supplied. Etiology, morbid anatomy and histology, morbid physiology, as well as the symptomatology, diagnosis, prognosis, treatment and prevention are discussed. The book will be found invaluable by the elementary student. Clinicians of experience will be interested in the chapters on physical signs, course and prognosis, since their subject matter is based on the author's extensive observations. The studies on the course of the disease constitute a very important contribution. C. W.

THE ACTION AND USES IN MEDICINE OF DIGITALIS AND ITS ALLIES. By ARTHUR R. CUSHNY, M.A., M.D., LL.D., F.R.S., Professor of Pharmacology in the University of Edinburgh. Pp. 303; 77 illustrations. Longmans, Green & Co., 1925.

THOSE who are acquainted with Cushny's *Pharmacology* and his monograph on "The Secretion of the Urine," are well aware of his breadth of view, clarity of expression and ability in critical analysis. His new book, on a subject in which he has been particularly interested for many years, and on which a great amount of work has come from his laboratory, is of the same high standard as the others. The writer has long been recognized as the outstanding authority on digitalis, and this book, therefore, may be considered the most authoritative account that can be written at the present time.

The book is most comprehensive in its contents and scope. It begins with an historical account of the use of the digitalis group in medicine. The second chapter deals with the chemistry of the group, and the present state of knowledge of this confusing subject is clearly stated. The basic principles of digitalis action are

described in detail in a chapter on its action on the frog's heart, and from this the author passes to the action on the mammalian heart, a subject on which he is particularly well versed through his own work. This pharmacologic section might well serve as a model for orderly sequence, completeness and clearness in presentation.

The use of digitalis in therapeutics is discussed at length. The author's collaboration with Mackenzie has given him a first-hand knowledge of digitalis therapy, and the chapter on this phase of the subject, dealing with the mechanism of digitalis action in the various forms of cardiac disease, is of great practical interest. The book ends with a chapter on administration and a critical analysis of current methods of assay. The extensive bibliography given, which includes practically all the important contributions to the subject, will be invaluable to workers in this field. An engraving from a portrait of William Withering serves as a frontispiece. The illustrations are abundant and unusually well done.

The book is remarkable in the well-rounded and even way in which all sides of the subject are presented. It will be read with the greatest profit by all students of medicine and particularly by those who are working on cardiac disease. G. W.

NEUERE ARZNEIMITTEL: IHRE ZUSAMMENSETZUNG, WIRKUNG UND ANWENDUNG. By PROF. DR. MED. C. BACHEM, Instructor in Pharmacology, University of Bonn. Third edition. Pp. 141. Volume 669 of the Göschen Collection. Berlin and Leipzig: Walter de Gruyter & Co., 1925.

THIS little volume states briefly the composition, action and therapeutic use of a large number of therapeutic agents that have been put on the market during the past fifteen years. Particularly in Europe has there been a flood of such drugs, usually under trade names, and many of them have found a vogue and fill a useful place in medical practice. For the most part only drugs that have shown themselves to be of practical value have been included in the book. It is unfortunate, however, that the author was not a little more critical in some instances: for example, an insulin preparation for oral administration. R. K.

CLINICAL FEATURES OF HEART DISEASE. By LEROY CRUMMER, M.D., Professor of Medicine, University of Nebraska. Pp. 353. New York: Paul B. Hoeber, Inc., 1925.

THE author's discussion is limited almost exclusively to the purely clinical aspects of heart disease. Nearly one-fourth of the book is

devoted to history-taking, inspection, palpation, percussion and auscultation, and only twelve pages to mechanical aids in diagnosis. The style is extremely attractive, clear and easy to read, and the subject-matter is presented in an interesting, even fascinating manner. It is all the more regrettable therefore that the book has serious faults requiring mention. Many statements are made in an unjustifiably categorical manner. Opinion is sometimes presented as though it were established fact. Far too many misstatements are found, such as the following: "Paroxysmal tachycardia, flutter and profound fibrillation are quite unknown in aortic insufficiency." It is of course well known that auricular fibrillation is not infrequently found in hearts with aortic insufficiency, with or without associated mitral valvulitis.

The book will be read by experienced students of heart disease with interest, pleasure and profit, but it does not distinguish sharply enough between opinion and established fact to be unreservedly recommended for the beginner. C. W.

MEDICAMENTS ET MEDICATIONS CARDIAQUES. By H. VAQUEZ, Professeur a la Faculté de Médécine de Paris. Lectures collected by M. Theodorescu. Pp. 302. Paris: J. B. Baillière et Fils, 1925.

THE author states that these lectures were primarily designed for the instruction of the assistants in his service. At the request of M. Theodorescu he consented to have them written and published. The drugs employed in heart disease are adequately discussed, as is the hygiene of the cardiac. The latter half of the book is devoted to the treatment of the various clinical manifestations of heart disease. The arrangement of the lectures makes information desired on any subject readily accessible. The book easily ranks as one of the best on the treatment of heart disease. It is to be hoped that an English translation will be made. C. W.

AN INTRODUCTION TO SEXUAL PHYSIOLOGY. By F. H. MARSHALL, F.R.S. Pp. 167; 72 illustrations. London: Longmans, Green & Co., 1925.

BEGINNING with the methods of reproduction in the lower animal forms and progressing to similar functions in the mammals, this book considers the physiology of reproduction in a satisfactory manner. Chapters on Heredity, Fertility and the Internal Secretions enhance the value of the volume, and it should be of assistance to students of medicine and biology, more particularly the latter. F. B.

A Synopsis of Gynecology. By Arthur Gray, F.R.C.S., M.R.C.P., Gynecological Surgeon, Hampstead General Hospital. Pp. 352; 7 illustrations. London: Edward Arnold & Co., 1925.

This book is not designed to be a general textbook, but is written in the form of a syllabus. The material is based on the author's lecture notes and is so condensed into important headings and subheadings, with brief but valuable comments, that it is ideally suited for students preparing for examinations as well as for instructors who wish to quickly review the subject. A little too much attention is paid to endometritis which is now admittedly a rare condition. The author apparently has not been won over to the use of radium in cancer of the cervix, as he advises operation in all but advanced cases. F. B.

Diseases of the Ear, Nose and Throat. By Harold Hays, M.A., M.D., F.A.C.S., City and Riverside Hospitals, New York City. Pp. 969; 550 illustrations. Philadelphia: F. A. Davis Company, 1925.

The author has prepared this work especially for the use of the student and general practitioner. The problems of otolaryngology are admirably presented in a clear and commonsense manner. Of particular merit is his chapter on Progressive Deafness, in which he emphasizes the importance of careful supervision and treatment of the partially deaf child. Not only will the student and practitioner be benefited by the information this book contains but the internist, pediatrician and otolaryngologist will do well to give it their attention. K. H.

Hereditary Disorders of Bone Development (Part I). By Percy Stocks, M.D., D.P.H., with the assistance of Amy Barrington. Pp. 182; 16 plates. London: Cambridge University Press, 1925.

This is one of the memoir series from the Francis Galton Laboratory for National Eugenics, and is Volume III of *The Treasury of Human Inheritance*. The disorders of bone development showing tendency to hereditary transmission dealt with are multiple exostoses (diaphysial aclasis), multiple enchondromata, cleidocranial dysostosis, congenital dislocation of the radius and rare conditions designated "la pléonostéose familiale" and "hereditary osteitis."

The data is treated statistically, with emphasis on hereditary

influences. Pedigrees of 210 families are diagrammatically represented. The main anatomic and pathologic features are illustrated in nine plates, supplemented by brief descriptions of normal bone development and the pathology of the conditions treated.

A bibliography of 1050 titles is reviewed. Karl Pearson, in the introductory note, asks for more subscribers to the series. Volume II of the *Treasury* deals with hereditary diseases of the eye, and is partly published. R. A.

STATISTICAL METHODS FOR RESEARCH WORKERS. By R. A. FISHER, M.A., Fellow of Gonville and Caius College, Cambridge; Chief Statistician, Rothampsted Experiment Station. Pp. 239; 10 graphs; 67 tables. Edinburgh and London: Oliver & Boyd, 1925.

BIOLOGIC research is characterized, as a rule, by smaller groups of observations than those usually submitted to statistical analysis. This has stimulated the preparation of this book, which stresses particularly the statistical methods applicable to biologic problems. No one unfamiliar with the technic and terminology of statistical methods will be able to follow the full sense of the text without arduous study of its pages. However, a merit of the book is the wealth of examples illustrating the application of the various methods to particular biologic problems and from these examples some appreciation of the place of these methods in biologic research may be easily obtained. J. A.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

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A Clinical Classification of Bright's Disease.—The varied classifications of Bright's disease offer one of the difficulties to the proper understanding of the disorder which presents itself to students, and clinicians as well. Until there is a well-comprehended, thoroughly established nosology of the several types of kidney disease the study of the disorders of this organ will not be on the same high plane as the studies of the heart, for example, or of the infectious diseases. If the student cannot understand just what an author means or what his language implies exactly confusion is bound to be present. The trouble in recent years has been that the internist is dissatisfied with the anatomical diagnosis made by the pathologist because, as THOMAS ADDIS (*Jour. Am. Med. Assn.*, 1925, **85**, 163) writes, his observation is limited to one moment of time and that moment the last of life. To obviate the discrepancies between the clinical picture of Bright's disease and the pathologic findings resource has been had to the so-called functional diagnoses. Pathologists may differ in their conception of the microscopic lesions, but how much more do clinicians differ when they attempt a classification of the protean disease upon any one of a number of disturbances in function of the organ or upon some outstanding symptom. The present article would seem to add even greater confusion to the present-day mixture of anatomical, functional and symptomatic diagnoses of kidney disease. This is the chief

criticism of an otherwise extremely able presentation. Addis classifies Bright's disease as hemorrhagic, degenerative and arteriosclerotic. The first type is subdivided into initial, active, latent and terminal stages. The criteria upon which this classification is based are the number of red cells, the epithelial and white cells, the casts and the milligrams of albumin in specimens of urine. Collected under certain well-controlled conditions, and examined by the special technic of the author, neither the control of the patient nor the methods of examination of the urine apparently offers any serious obstacle to the physician; therefore, the simple and lucid classification of the author has distinct advantages. However, until the methods of the author are extensively used and found practical to use it would not seem wise to employ the new classification of Bright's disease in textbooks, current literature or in the teaching of students.

Puncture of the Cisterna Magna: A Summary of Four Years' Experience.—Puncture of the cisterna magna was first described by Ayer, in 1920, as a clinical procedure of value in certain cases of meningitis. F. G. EBAUGH (*Jour. Am. Med. Assn.*, 1925, **85**, 184) promptly saw the advantage of this method of securing cerebrospinal fluid or of introducing therapeutic agents into the canal, and has employed it extensively the past five years in his neurologic work at the Philadelphia General Hospital. The present paper is a general report of the 1550 punctures of the cisterna magna in a total of 190 patients that the author has done in the above mentioned time interval. He states that after a certain amount of practice on the cadaver the operation is easily and readily performed. In all his cases only 2 patients showed any possible but questionable ill results after the puncture. Forty patients were examined after death without evidence of pathologic changes, and 1 of these patients had 26 intracistern injections. The clinical indications for puncture of the cisterna magna are summarized by the author as (1) therapeutic, (2) diagnostic and (3) prophylactic. Under the first head is included 1340 punctures for the purpose of injecting arsphenaminized and tryparsaminized serum in treatment of general paresis; 32 injections of antimeningococci serum in 8 advanced cases, with recover of 5 patients; 54 punctures for therapeutic drainage; 2 punctures for the unsuccessful treatment of a patient with tetanus. Under diagnostic use of cisterna puncture are listed 20 punctures in 15 cases of which 7 showed definite findings of spinal block verified at autopsy or operation; 3 punctures for the localization of spinal-cord tumors through use of lipiodol; 4 cases for the localization of site of hemorrhage; 27 cases in which lumbar puncture was impossible. The prophylactic use of this procedure is to prevent possibility of block following meningitis. In discussing more in detail these figures the author writes that the use of arsphenaminized serum in the treatment of neurosyphilis has been discontinued on account of the failure to achieve any beneficial effects. He says that the treatment of meningitis by alternate intraspinal and intracistern puncture offers a method of getting the greatest concentration of serum into the cerebral and spinal subarachnoid space and avoiding subarachnoid block. This suggestion, and it is largely a suggestion as the author has not had the opportunity of trying out this procedure at all extensively, is apparently an extremely practical one.

SURGERY

UNDER THE CHARGE OF

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A Critical Study of Endocrine Therapy in Gonad Failure in the Male.—LAWRENCE (*Boston Med. and Surg. Jour.*, 1925, **192**, 480) noted that the clinical picture produced by ablation or depression of the endocrine function of the male gonad is not constant. The variations are probably due largely to the age at which the failure occurs. Eunuchoid states are frequently due to secondary gonad failure which is a result of some other endocrine dysfunction, notably the pituitary. The treatment of such conditions by use of testicular extracts or implants cannot be expected to give good results. Therefore, every patient showing eunuchoid symptoms should be carefully examined for evidences of other endocrine disease before testicular organotherapy is advised. If such treatment is indicated it is best obtained by implantation of human testicular substance. The treatment of such conditions as senescence, sex lassitude, dementia precox, epilepsy or general asthenia by gonadal extracts has no logical basis and is not at present justifiable. There is no definite evidence that the use of testicular extract in tablet form has any specific effect in man. Endocrine therapy of gonad failure in the human male cannot become an established form of treatment until the effects of such failure upon bodily processes has been determined by objective measures and the value of therapy proven by demonstrating its effects in the same way. At present the conditions for which organotherapy is indicated are limited to the results of castration and certain eunuchoid conditions.

Is there an Essential Hematuria?—SCHEELE and KLESE (*Arch. f. klin. Chir.*, 1925, **130**, 388) state that this concept has lost its significance in the light of newer pathologic, anatomic and clinical observations Bleeding in the parenchyma comes from glomerular and interstitial sources. The areas of the papillæ and pelvis have mechanical inclination or disposition to bleed, due to the arrangement of tissue elements. The rich subcapsular lymphatic network offers definite cause for bleeding from the capsular area. For bleeding to arise from nerve origin there are the peristaltic movements of the capsule and the definite hyperemia of the kidneys under nervous influences as factors. The mechanical interruption of the kidney circulation either through venous pressure or back pressure of the urinary tract, can lead to hemorrhage. There is blood from the kidneys in hemophiliacs. This hemorrhage however, is present only in men who show the other signs of hemophilia. Hemorrhage and pain show no typical course, therefore

they are not significant alone for diagnosis. The authors analyze the conservative and radical operative procedures at length. Only in life-destroying hemorrhage, do they feel that primary nephrectomy is indicated.

The No-foreign Body and Tight-fitting Window-cast Technic in Open Reduction of Fractures.—SORESI (*Jour. Bone and Joint Surg.*, 1925, **7**, 289) states that open reduction of fractures by the no-foreign body and tight-fitting window-cast technic represents an advanced step in the treatment of fractures. In the cases in which the method was applied results have been very satisfactory; none of the complications common to the other methods of open reduction, such as infection, osteomyelitis, necessity of removing the foreign bodies used for osteosynthesis, delayed union, painful limbs or death were observed. In cases where infection was present no unpleasant complication was noted. The results were as satisfactory as in the clean cases. This fact demonstrates that complications noted where other methods are followed are due to the presence of the foreign bodies used in the process of osteosynthesis. It follows that foreign bodies prevent the proper formation of callus and favor infection, while direct good coaptation of the fractured ends of the bone, presence of blood, complete absence of foreign bodies in the wound mean better union, because callus formation is not hindered. Contrary to the generally accepted opinion, bones can stand a great deal of trauma and infection, the ordinary usual complications following trauma and infection being due to the presence of foreign bodies which are injurious to the process of bone repair.

On the Viability of the Intestine in Intestinal Obstruction.—ELSBERG (*Ann. Surg.*, 1925, **81**, 926) believes that it is often difficult to determine the viability of strangulated intestine, although there is a rich anatomosis in the mesentery and intestinal wall, comparatively slight interference with this circulation causes disproportionately great damage to the intestine. Experimental ligation of the vessels of the second mesenteric arcades is the safest. The circulation returns or becomes reëstablished in an impaired segment either through the temporarily occluded vessels, or as the result of a collateral circulation. The circulation does not return and the segment becomes gangrenous if the involved area is too large and there is too great a trauma to the vessels with a prolonged spastic muscular contracture. The classification of strangulated bowels into early, intermediary and late does not designate units of time. This depends upon the size of the segment, its proximity to the duodenum and whether the circulation is immediately or gradually occluded.

Syphilis of the Urinary Bladder.—SAELHOF (*Jour. Urol.*, 1925, **13**, 461) says that the pathological anatomy of vesical lues has been studied by suprapubic cystotomy, cystoscopic examination and autopsy. It may be readily apprehended that the pathologic anatomy evident in the bladder wall is essentially dependent upon the stage of the disease in general. In the author's case the intensely hyperemic mucosa with ulcerations eccentrically located about the mouth of the left ureter led to a diagnosis of syphilis of the bladder. Under intensive antiluetic

therapy the bladder symptoms disappeared. However, under the delusion that he was cured, the patient failed to continue treatment and a subsequent relapse with return of bladder symptoms again became manifest. Death ensued from a bronchopneumonia complicated by cerebrospinal lues. Microscopic sections of the bladder revealed a picture essentially that of lues of any organ of the body, namely a marked proliferation of lymphocytes and round cells, proliferation of fixed cells and more or less endarteritis.

Abdominal Torsion of the Omentum.—COWELL (*Brit. Jour. Surg.*, 1925, **12**, 738) declares that torsion of the omentum is commonly associated with the presence of hernia. True intraäbdominal torsion, however, does exist, although it is rare. The following simple classification of torsion of the omentum is suggested by the author: Abdominal; primary, with no apparent cause present; secondary, associated with disease of an abdominal or pelvic organ; hernial: (*a*) intersaccular, (*b*) intraäbdominal, (*c*) combined. Clinical recognition is possible and operative treatment successful. The pathogenesis is uncertain, but obesity is a factor in some cases. Torsion of the omentum should be one of the conditions suspected when a rush of blood-stained serum occurs during a laparotomy on an acute or subacute abdomen. The adhesions readily give away and the mass is easily removed by ligaturing the pedicle. The mortality is low, namely 5.5 per cent, and no complications have occurred in the author's series of 18 cases.

Carcinoma of the Rectum Complicated by Pregnancy.—MAUNSELL (*Brit. Med. Jour.*, 1925, **3357**, 826) claims that there are two "schools" of rectal surgery. One advocates the perineal route for excision, while the other despises anything except the combined abdominal and perineal operation. The author feels that the two-staged operation is much easier and feels that it is the method of choice where pregnancy is a complication, unless there is some special reason for the one-staged operation. The author feels that the incision through the left rectus is best for colostomy, either with or without a median incision for the exploration. With regard to the treatment of carcinoma of the rectum in general, the author sometimes uses the combined method, but more often the perineal, with removal of the coccyx and the last segment of the sacrum, a thorough exploration and a colostomy having been made some days previously. He is convinced that the mortality of the combined method is very much greater than that of the two-stage operation, while the percentage of "cures" is not more pronounced in one group than the other. The author's teaching is to remove the growth by the two-staged method, when it is in the portion of the bowel which has no mesentery. When the growth is situated higher up it is better to remove it by the combined method.

Elbow Fractures and Dislocations.—SIRIS (*Surg., Gynec. and Obst.*, 1925, **40**, 665) claims that children have excellent reparative powers in fractures. Perfect anatomic approximation of the fragments is not always essential for functional recovery. Displacement and overriding of fragments will often result in a good functional limb and complete restoration of the bony contour. Anatomically restored elbows may

be lacking in mobility unless they are treated judiciously. The best results are obtained by immediate reduction under an anesthetic with the aid of the fluoroscope. Partial immobilization with adhesive and early active motion will reduce swelling, increase muscular toxicity and prevent muscular spasm, exuberant callus, Volkmann's ischemic paralysis and myositis ossificans. Passive motion with or without an anesthetic and active massage retards progress. Musculospiral and ulnar paralysis accompanying the following fractures about the elbow is now always permanent. Myositis ossificans will disappear with the discontinuation of trauma to the bronchialis anticus. Open operations in children are not indicated, as good functional limbs will follow displaced fragments and infections are very prone to follow open operations. Compound fractures are best treated by debridement. Carrel-Dakin sterilization, suspension in flexion by adhesive or in a flexed Thomas splint, to be followed by secondary suture or granulation with the institution of early active motion.

Movable Kidney.—MATHÉ (*Surg., Gynec. and Obst.*, 1925, **40**, 665) states that the great majority of movable kidneys cause no symptoms and require no treatment. In a certain percentage of cases, however, renal mobility forms a definite clinical entity characterized by lumbar pain, urinary, gastrointestinal and nervous disturbances, loss of weight and require fixation by abdominal support or surgical intervention. The condition is more common in females because the renal fossæ are shallower, cylindrical or even funnel shaped, being wider below than above. The predisposition to displacement is increased at puberty because of the widening of the bony pelvis. In males the renal fossæ are pear shaped, being narrower below. Its greater frequency on the right side is due to the shape of the renal fossa, the presence of the liver on that side and the weaker support afforded by the less well-developed right, perirenal fascia. The majority of cases of renal ptosis can be relieved by the proper abdominal support, fattening and strengthening exercises. Nephropexy is a justifiable operation and is indicated in conditions not relieved by more conservative measures. The author has employed nephropexy in 30 cases, with successful results in 96 per cent of the cases; 46 per cent of these cases had obtained no relief from mechanical supports. A review of the literature leads the author to believe that surgical suspension has fallen into disrepute, not on account of its inefficiency, but because it has been performed when it has not been indicated. Moreover there is often failure to realize the necessity of exposing the ureter and relieving any condition which might be present, which unrelieved would defeat the purpose of the operation.

The Treatment of Acute Pathogenic Joint Infections.—BLAKE (*Am. Jour. Surg.*, 1925, **39**, 81) states that the story of the treatment of pyogenic arthritis resembles in many ways that of suppurative peritonitis and empyema of the thorax. Surgeons now know that the same principles apply to the treatment of all cavities. These concepts are in the main: That resolution usually usually follows if the origin or cause of infection is removed before pathologic changes have taken place in the deeper tissues. Traumatism, leading to death

of tissue, prolongs suppuration and prevents resolution. Foreign bodies, such as drains, produce traumatism. Accumulation of the products of infection not only delay absorption, on account of their bulk, but by pressure in the rigidly enclosed cavities, such as joints, interfere with circulation and may cause thrombosis of vessels and necrosis of tissue, not to speak of toxins from the exudates. When suppuration of a joint is produced by extension from a focus in a bone or from an infected fracture implicating the joint it is obvious that the primary lesion in the bone must be well-laid open and drained, so as to prevent, so far as possible, contamination of the joint. Such joints should be kept at rest to prevent spreading the infection throughout the articulation. In the case of the knee the condition may become formidable and amputation should not be deferred to the point of danger to life. This amputation should be done in two stages to avoid the danger of osteomyelitis of the stump. The author describes in generalities the treatment of primary suppurative processes in joints, stressing as the ideal time the first twelve hours after injury, in which there is practically no pullulation of bacteria, and a thorough trimming away of contaminated and devitalized tissues will prevent infection or modify its virulence. No drain should be used. Early active movements should be instituted in joints where mobility is desirable.

PEDIATRICS

UNDER THE CHARGE OF

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Supervision of the Dairy Herd to Prevent Anaphylactic Symptoms in Infant Feeding.—ROHRBACH (*Atlantic Med. Jour.*, 1925, **29**, 670) has been unable to find anything written on this subject in any of the available indices. Evidence that cow's milk produces anaphylaxis is admitted by many eminent authorities. These symptoms are referable to practically every tissue of the body. The family history often reveals a characteristic hereditary tendency to be sensitive. Cow's milk is tolerated with great difficulty by 15 per cent of well and sick infants. This intolerance is manifested by a positive skin reaction in some infants and a negative one in others, whether artificially fed or breast fed. If allergic disturbances are changes in the physical and chemical mechanism of the blood and tissues, thereby bringing about an altered state of physiologic functions then it is believable that similarly the food of the dairy animal producing milk for infant feeding is a source of frequent anaphylactic symptoms and that the clinical symptoms of the cases reported in this paper are typical allergic reactions to such foods. It is a sad but true fact that no interest at all, it might be said, is taken by the medical profession in the production of milk for human consumption.

The Ketogenic Diet in Epilepsy.—PETERMAN (*Jour. Am. Med. Assn.* 1925, **84**, 1979) used the ketogenic diet which consists of a large amount of fat with minimal amounts of protein and carbohydrate. The object of the diet is to produce a ketosis as evidenced by acetone and diacetic acid in the urine. It is especially desirous to stress this objective. He treated 37 patients with essential epilepsy for periods of from three to thirty months by means of this high fat diet sufficiently restricted in carbohydrates and proteins to produce ketosis. In 2 patients no change was noted. One patient improved while under control but was lost from observation. Three patients remained free from convulsions for from three to eight months, and were not heard from. Twelve had improved and 19 had been free from attacks since the institution of this treatment. Thirty-two still remained under observation at the time the report was made. The general physical development and growth had also been normal and exceptionally good in some cases. Resistance to infection seems no way diminished by this form of treatment. It is too early to offer an explanation for these results. Much work is necessary, and a better understanding of ketosis is essential. The theory under which this high fat treatment of epilepsy was first proposed was that aceto-acetic acid should behave pharmacologically as an anesthetic and reduce the reactivity of the nerve cell. It is sufficient to say at present that ketonuria with the high fat diet is a practical guide to treatment, even though it is not the only factor concerned in metabolism. Acidosis is possibly a factor in controlling the attacks. There is considerable evidence that the convulsions of epilepsy are associated with a metabolic disturbance. The capricious and inordinate appetites, the chronic constipation and history of stomach troubles and of food reactions, the periodic recurrence of attacks, the nature of status epilepticus, the increased toxicity of the urine obtained during the attacks, and in women the cessation or the primary appearance during pregnancy, all suggest coincident, if not primary metabolic disorder. Perhaps the most convincing evidence of metabolic disturbance is the response of the epileptic patients to treatment. In the earlier cases of pure idiopathic epilepsy in children the response to the treatment with ketogenic diet was striking. The results obtained by hydrotherapy, purging, by regularity of daily habits or best by a combination of all these adjuncts need no further mention. Psychotherapy is not to be overlooked.

Diphtheria of the Skin.—WARREN and SUTTON (*Jour. Am. Med. Assn.*, 1925, **84**, 1983) report the case of a boy, aged five years, in whom the skin lesions of varicella took on an impetiginous character and became infected with Bacillus diphtheriæ, probably transferred from the nostrils by scratching. They gradually progressed to extensive hemorrhagic crusted lesions covering about 49 sq. cm. of body surface. Death apparently was due to toxemia, and the necropsy findings were consistent with infection with Bacillus diphtheriæ. Virulent diphtheria bacilli were recovered from the skin at least in one lesion, and the histologic picture of the lesion is that of diphtheritic ulceration. Sections stained by the Gram-Weigert method showed bacilli morphologically resembling Bacillus diphtheriæ. In short in this case there were the microscopic findings consistent with toxemia due to infection

with the diphtheria bacillus, together with typical diphtheritic ulcerations of the skin. In addition, the recovery of virulent diphtheria bacilli from the nostril and from one of the skin lesions definitely stamps the case as one of diphtheria. The virulence of the bacilli was determined by the intracutaneous method. The guinea pig on whom the virulence test was done died on the fifth day after inoculation. Necropsy on this animal showed that death was due to diphtheria. The control pig protected by 1500 units of antitoxin was not affected. The Schick test was done on this case on admission, and was negative. This is a surprising finding in view of the subsequent death from diphtheria. The absence of membrane in the nasopharynx and the development of symptoms only as the skin lesions became infected led the authors to believe that the toxemia resulted from the diphtheria of the skin. Some of the lesions of varicella in all probability were infected from scratching with fingers that were infected with virulent bacilli from the nose.

Cerebrospinal Fluid in Syphilitic Children.—VON GUTFELD and MEYER (*Arch. f. Kindhk.*, 1925, **76**, 13) made systematic examinations of the blood and cerebrospinal fluid in 155 syphilitic children, and they found a Wassermann reaction parallel to the clinical findings only in a part of the cases. In cases of mental and nervous disturbances a positive reaction was found in the cerebrospinal fluid more often than a negative, but the reaction may be positive without such disturbances or *vice versa*. Positive blood tests usually correspond to a positive reaction in the cerebrospinal fluid, but the reverse does not hold true. The colloidal gold test in the fluid elicited a reaction parallel to the Wassermann test in almost every case. Endolumbar treatment was never used. The clinical findings alone afford definite indications for treatment.

Congenital Hypertrophic Pyloric Stenosis.—BOLLING (*Jour. Am. Med. Assn.*, 1925, **84**, 20) reviews 454 cases in which the Fredet-Rammstedt operation was performed. As to diagnosis, he feels that if the condition is kept in mind the diagnosis may be made promptly in almost every instance, and is not a matter of opinion but is demonstrable. A palpable pyloric tumor and a gastric peristaltic wave in combination occur in no other condition. The history if obtained from an intelligent nurse or mother is valuable and often typical. There has been some discussion as to the diagnostic value of the tumor. The author thinks it is the most important sign. The palpation of the tumor is most easily carried out after the stomach has been emptied by means of a soft rubber catheter, and while the child is kept quiet with its usual feeding or a sugar pacifier. Usually lying to the righ hand of and above the umbilicus, the nodule may be made out high up under the liver or even in the midline, just below the ensiform cartilage. It is a small, oblong, movable mass, about the size of the distal phalanx of the little finger, and imparts a sense of almost cartilaginous hardness through the abdominal wall. The consistency of the tumor varies as the muscle comprising it is contracted or relaxed. At the

time of relaxation the pylorus may be stimulated by gentle kneading with the finger. The more emaciated the infant, the more obvious the tumor. In early cases in which there has been little loss of weight it is more difficult to make out, but patient examination will almost invariably be rewarded. In the 454 cases operated on it was felt in every instance but 1. During the same period there were 3 cases in which anteoperative diagnosis of a tumor proved incorrect. Deep, regularly occurring peristaltic waves, passing from left to right, may be seen in practically every instance if the epigastric region is inspected after the stomach is filled and while the child is quiet. These waves were observed in all but 3 cases of the series. Congenital occlusion of the duodenum may give a similar picture, but this condition is rare, and the presence of symptoms from birth and the bilious character of the vomitus serve to differentiate it from the pyloric involvement. The significance of peristalsis depends on degree. Slight peristaltic waves may be seen in even normal infants. The characteristic projectile vomiting is frequently observed during the examination. The secondary symptoms of loss of weight, constipation and scanty urine are merely evidences of starvation. The author thinks that roentgen-ray is indicated only in doubtful cases. Fluoroscopic examination is the most important means of making an accurate diagnosis and it not only shows whether the condition is pyloric stenosis, but classifies it immediately as a medical or a surgical case. It was found from a study of this series that the Fredet-Rammstedt operation is simple, curative and permanent in its result. Convalescence is rapid, and the infant returns almost at once to normal development. The constant progressive decline in mortality suggests further improvement in this direction. He feels that as a result of the finding in this analysis that there is no justification for delay which turns a good operative risk into a bad one substitutes a long accidental convalescence for a brief, uneventful one, and fails to restore the growing infant to a satisfactory state of nutrition at an important period of its development.

Tuberculous Meningitis in Children.—HERBEN and ASSERSON (*Am. Rev. Tubere.*, 1925, **11**, 184) made a very careful analysis of all the circumstances and facts connected with a series of 135 cases of tuberculous meningitis in children. In almost all of these cases the cause of the disease was the human type of tubercle bacillus derived through the child's contact with persons suffering from active tuberculosis. This form of infection is most prevalent in the least sanitary and most congested districts, and tenement houses present a most formidable aspect among etiologic factors. The evidence is predominatingly against milk infections as a cause of tuberculous meningitis in New York City. Otitis media and acute infectious diseases, especially measles, pneumonia and whooping cough in children in contact with active tuberculosis, carry a great menace. About 9 per cent of these 135 cases were preceded by tonsillectomy, unassociated with any other disease. Sex is not an important factor, males being only slightly in preponderance. The highest mortality occurred in young children, the greatest number of cases in a single age period developing in childhood from one to two years of age. In terms of absolute numbers only,

outside of the American stock, there was more tuberculous meningitis among the Italians than in any other racial group. While this study verifies the accepted view of the great prevalence of tuberculous meningitis in the spring, this disease among the Jewish and negro races reached its peak in midsummer. In 47 specimens of spinal fluid showing tubercle bacilli the latter were bovine in type in only 3 instances

GYNECOLOGY

UNDER THE CHARGE OF
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Irradiation of Benign Uterine Tumors.—About three years ago in the Cleveland Clinic, according to PORTMANN (*Jour. Iowa State Med. Soc.*, 1925, **15**, 3), they began the investigation of deep roentgen-ray therapy. In collaboration with the department of biophysics a special study of the intensities of roentgen rays was made, and the findings were compared with the results already published. They were disappointed to find that the very great dosages anticipated were not obtainable under practical working conditions, and as a result they came to the conclusion that in most cases a therapeutic dose of radiation could not be safely administered to the most deeply situated malignant tumors by roentgen ray alone. The favorable results of radium therapy and this knowledge of the limitation of the roentgen ray led them to adopt a plan for the establishment of "a radiation therapeutic dose" by means of the combination of these two similar agents. This is accomplished by individualizing the patient by drawing on paper an exact cross-section of the body at the site of the lesion, and indicating thereon the involved areas and organs. Their own charts which show the rate of absorption of roentgen ray or equal intensity curves are superimposed on the cross-section at suitable portals of entry, so that the sum of the intensities of the roentgen rays which reach any point from the various portals may be calculated. A standard chart showing the sphere of radium activity is then superimposed at the point of radium application and the combined radiation from the roentgen rays, and radium can be computed for any point in the cross-section. By this method they are able to estimate and tabulate the exact dosage of radiation administered in any case. They have found that chronic metritis and fibromyomata react very favorably to proper administration of radiation in properly selected cases. Until recently the results of radiation in these cases have varied considerably, but since they now have accurate methods of measurement, and a basis for the selection of cases, they anticipate

more uniformity of results. In the selection of cases they believe that no woman under forty years of age should be subjected to radiation, as it tends to advance the menopause, although in certain cases there may be justifiable reasons for disregarding this precaution. Intensive radiation in the presence of chronic or acute inflammations or any evidence of inflammation within the pelvis is hazardous. Irregularity of the menses or the character of the bleeding may indicate a malignant or inflammatory degeneration of the uterus or of the tumor which would require a different method of treatment. A tumor of any size may be reduced by radiation, but those tumors that extend as high as the umbilicus may regress too slowly to relieve the rather distressing pressure symptoms. Pedunculated and subserous fibroids obviously demand surgical treatment. Pregnancy contraindicates radiation, as abortion will probably be induced, and it has been demonstrated that radiation may produce a monstrosity of the fetus. After eliminating the groups of cases indicated above as unsuitable for radiation there remain about 30 per cent of all cases of fibromyomata that may be safely treated by radiation. Relief of symptoms may be anticipated in 99 per cent of properly selected cases, and the percentage of complete cures averages about 87 per cent.

Cautery Treatment of Endocervicitis.—The use of the electrocautery in the treatment of chronic endocervicitis is surely enjoying increased popularity, judging from the number of enthusiastic reports which are appearing in the literature. One of the proponents of this therapy is DAVIS (*Surg., Gynec. and Obst.*, 1925, **40**, 568), who describes his technic as follows: After inserting a suitable bivalve speculum the mucous discharge is thoroughly removed with cotton balls. A suitable nasal cautery tip, preferably one longer than usually supplied, is placed firmly against the tissue to be destroyed and the current turned on. As a sufficient depth is reached in the cervical tissue along the cervical canal, the tip is gradually moved so as to make a line through the diseased tissue. In many cases it is only necessary to cauterize the glands near the external os; in others the disease extends to the internal os. If at any time the patient complains of discomfort the contact button is immediately released and the current not applied again until she is comfortable. This process is repeated until a sufficient number of cautery lines have been made. Nabothian cysts are destroyed in a similar manner after puncturing with the heated tip. An effort is made to reach the depths of the glands so as to destroy the chronically diseased tissue. Most cases of endocervicitis may be treated in the office. One thorough cauterization results in early relief from most of the symptoms, and complete healing is usually found after six to eight weeks. If the first treatment is very superficial another may be needed after four weeks. Very few patients will need more than two treatments with the cautery. As a rule, it is advisable to administer an anesthetic (gas and oxygen) to virgins, women who are very nervous or those who require unusually deep cauterization, due to the long duration of the endocervicitis. It may be difficult at times to remove tissue for examination unless the patient has an anesthetic. After a cautery treatment the patient is instructed to wear a pad until the increased discharge stops, which is usually in about ten days or two

weeks. She is also warned that the next period may be more profuse than normal, occasionally so severe as to require a pack for a few hours. Douches are advised against but the patient is advised to keep herself clean by external washing. The cervix is painted with 5 per cent mercurochrome solution every week until healing is complete. Sex trauma should be avoided during the period of convalescence from the cauterization.

Residual Urine in Women.—Previous to 1915, states CURTIS (*Surg., Gynec. and Obst.*, 1925, **40**, 689), when he first called attention to the frequency of residual urine in women, his patients had much trouble with postoperative urinary tract infection. After 1915, upon realization of the importance of residual urine, he instituted the present plan of postoperative treatment with most satisfactory results. Under his plan of treatment the use of the catheter is avoided when possible, but no patient is allowed to suffer from distention. Failure to urinate within several hours after return from the operating room is not, in itself, sufficient reason for catheterization; distress should be the chief indication. It is true that marked distention should be relieved, but this does not often occur in the absence of notable pain. Provided the catheter has not been required, the presence of some residual urine for a few days is not a particular menace. Patients who require repeated catheterization almost invariably fail to recover immediately the power of complete evacuation upon resumption of spontaneous micturition. There usually ensues a period of several days, during which residual urine is present, and it is the daily withdrawal of this residual urine which is responsible for the present improved results. Catheterization, immediately after urination, preferably with slight bladder lavage, should be repeated once each day until residual urine disappears. Instillation of a small amount of antiseptic solution before withdrawal of the catheter, for example, ½ ounce of 0.5 per cent mercurochrome is a helpful adjunct, together with urinary antiseptics by mouth. In contrast with previous experience, Curtis now finds that persistent postoperative urinary-tract infections have disappeared. Temporary mild cystitis may occasionally occur, but this is promptly disposed of. The much-dreaded "catheter" cystitis and pyelitis have been eradicated. We have followed this method of the author for some time in our department with very satisfactory results.

Value of Radiotheraphy in Uterine Cancer.—According to W. J. MAYO (*Minnesota Med.*, 1925, **8**, 7) radium has had its greatest triumph in the treatment of cancer of the cervix uteri. In the favorable cases radium is not only a compeer of the knife, but in the advanced case, when the vaginal fornix or the broad ligament is involved, it is the treatment of choice. The rays affect the embryonic cells with special vigor, while the sound tissues, such as the ureters, are little affected. On the contrary, in cancer of the body of the uterus, taking good, bad and indifferent cases, surgery cures from 70 to 80 per cent, and radium and roentgen-rays produce poor results. It has been a common experience in the clinic that even after radium had been used by experienced men in the body of the cancerous uterus for prolonged periods it was eventually necessary to remove the uterus, because some part of

it still contained malignant tissue. Unfortunately, the question of the curability of cancer is too often academic, because of the very large number of incurable cases that reach the surgeon, in which palliation is the utmost he can achieve. Here radiotherapy is, at its best, a triumph and a despair. It often does so much good that the family and the patient begin to look for and expect cure, but death, not cure, comes eventually, and radiotherapy is unjustly brought into disrepute after a meritorious performance. An unpleasant part of this discussion concerns the persons who are to use radium and roentgen-ray for the cure of cancer. When this work is done by men of wide experience, associated with an experienced surgeon and a competent pathologist, radiotherapy has great value. Today a large number of men with a small amount of radium, or with a roentgen-ray machine, are treating operable cancers or as has been said "With a nickel's worth of radium a million dollars' worth of harm can be done." The use of radium and roentgen-ray for therapeutic purposes is as much a specialty as surgery, but in the hands of the inexperienced, or of those who depend on the clinical diagnosis of the disease, it becomes a menace.

Stricture of the Ureter.—In a very well-prepared paper PUGH (*Ann. Surg.*, 1925, **81**, 839) states that a real stricture of the ureter is a definite, permanent, pathologic intraureteral obstruction which is present at a particular location and never varies from it, and is demonstrable not only by means of specially prepared catheters or bulbs, but by ureterograms as well. He insists that there is such a thing as ureteral spasm, which may simulate stricture and at times will interfere with examination. At times the resistance of these spasms is so great as to make us think that they are strictures, but a little pressure usually overcomes them. In discussing the etiology of ureteral stricture, the author divides the causes of stricture into the traumatic, into that caused by other infectious processes, the socalled focal infections, and that due to direct extension of disease processes. Traumatic strictures are most commonly incident to childbirth injuries or the performance of extensive gynecologic operations. The discussion of focal infections has been most extensive. If practically every acute infection may produce a lesion in another organ, there is no reason why it should not occur in the ureter. One of the predisposing diseases especially emphasized by Hunner is tonsillitis. In almost all of the cases in the author's series there was a record of some previous acute infectious process. Although Hunner does not lay much stress on the gonococcus as a cause, from the author's experience it is his opinion that the extension of a gonorrheal process from the urethra to the ureter is, at least in the majority of cases, by continuity of tissue and not by lymphatic conduction. In these cases the sequence is urethritis, trigonitis, ureteritis and stricture. It is not his intention to state that the gonococcus is the most common cause of ureteral stricture, but he believes that it is no uncommon factor in that disease. The symptoms of ureteral stricture are pain, which may be sharply localized at the point of stricture or over the kidney, the latter often being due to back pressure. There is often frequency and urgency of urination, and sometimes vesical or even rectal tenesmus may be present. Hema-

turia may be present, especially during severe attacks of pain. In some patients the pain is of a dull, aching character and present constantly, but the other and more common type is the periodic paroxysms. The referred group of symptoms are usually gastrointestinal. Chills and fever are common, particularly where there is distinct evidence of urinary infection. The main factors in establishing a diagnosis of stricture of the ureter are a careful history, the pyeloureterograms and the therapeutic result of treatment. An interesting point which has caused considerable discussion of late is the relation of stricture to stone formation. Does stone cause the stricture or may not the stricture cause the stone? The author is sure that a stone descending from the kidney and lodging somewhere in the ureter would obstruct it, but that does not spell stricture. On the other hand, he is thoroughly convinced that stricture does produce stone. He states that in these days of careful investigation it is unthinkable to operate for renal stone without a thorough exploration of both ureters for stricture, and he believes that this procedure, by establishing good drainage, will save many kidneys and repeated nephrotomies. The prognosis in ureteral stricture can in general be stated as good. It however depends to a great extent on the etiologic factors involved. Where syphilis is the underlying cause the prognosis should be good with appropriate treatment. In tuberculous lesions the outcome will depend on treatment; local applications or dilatations are of no value, nephrectomy or nephroureterectomy being required. In the other forms of stricture the treatment consists of removing the cause if possible, and dilatation of the stricture through the cystoscope. In the use of ureteral dilators one should be careful not to dilate both sides (where bilateral stricture exists) at one sitting. Where this is done the trauma may produce contractions that will seriously delay treatment. Care must also be exercised that one does not puncture the ureter. The degree of dilatation necessary will depend entirely on the individual case, but we should dilate until we get good drainage which seems to be reasonably permanent. Operative treatment of stricture is unsatisfactory, and, like all other ureteral surgery, should only be resorted to as a final expedient.

Irradiation of Inoperable Cervical Cancer.—In describing the more recent methods of irradiation in the treatment of inoperable cervical cancer. DONALDSON (*Brit. Med. Jour.*, 1925, i, 876) says that, speaking generally there are two schools of technic: One which believes in external application only; the other which believes in burying the radium close to or within the growth. The arguments for the different opinions may be summarized as follows: The advocates of external application consider that any incision, even the introduction of needles, may disseminate the growth, and that the injured normal tissues may be affected by the radium to an undue extent, as it is well known that radium affects cells which are about to go into mitosis. They also believe that the tissue extracts produced by injury to the normal cells may stimulate the growth of the tumor and that the burying of needles may produce sepsis under conditions very suitable for the growth of organisms. Those authorities who advocate the burying of needles do not consider that these objections are in any way compar-

able to the advantages of the greater intensity obtained by placing the needles near the growth, and, further, that if the radium is used from the outside the doses have to be so large that there is considerable likelihood of damaging the skin and other intervening structures. The Radium Institute of Paris is inclined to believe in external application as is the Radium Institute in Stockholm, while in Brussels and most of the American institutes buried radium is preferred. In Great Britain the opinion is divided. The author's own opinion is that any technic should aim at getting a comparatively small intensity evenly distributed throughout the growth and applied for a comparatively long time. The question of the best dosage is still *sub judice*, but we must remember the fact that the intensity of radium obeys the inverse square law in the same way as does light. As an illustration, it may be noted that the dose received by the fingers holding a tube of radium with a filter of 5 mm. of platinum for a half minute is the same as if those fingers were exposed at a distance of one yard from the radium for a period of three and one-half years, or, to put it in a more practical form, the tissues in the pelvis 2 inches away from the tube receive 10,000 times less irradiation than the tissues immediately surrounding it. In regard to the duration of application, the author believes that the clinical evidence is very much in favor of a medium dose, well distributed and applied for a very long time, and in his last series of cases he has been using 50 mg. of radium element in twenty needles for one hundred and forty-four hours at a time, with distinct improvement in immediate results, compared with his former series. In analyzing his latest series of cases he finds that the hemorrhage ceased more or less permanently in 85 per cent, the ulceration disappeared in 63 per cent and in the cauliflower type the growth disappeared in 70 per cent.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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A Microscopic Study of the Excised Tonsil in Relation to Tonsillectomy.—Desiring to demonstrate the existence or nonexistence of the true "tonsil capsule;" whether or not the removal of the tonsil could take place without injury to or removal of some adjacent voluntary muscle tissue; the influence of the latter on the end-result of the healing, scar-tissue formation and deformity, as well as to briefly shed some light on the bloodless tonsillectomy, ISRAEL (*Ann. Otol., Rhinol. and Laryngol.*, 1925, **34**, 79) studied, microscopically, about 500 sections from 172 tonsils, removed according to eight different methods by laryngologists of recognized skill in various parts of America. It was found that comparatively few tonsils were removed without some muscle tissue attached, the largest amount of muscle tissue appearing on the lateral surfaces of the atrophic type of tonsils in adults. Larger

tonsils, particularly in children, showed muscle tissue consisting chiefly of part of the palatoglossus and mucous membrane of the anterior pillar. No true capsule, which could be separated as a definite independent structure, could be identified as such. The amount and type of bleeding were found to be dependent chiefly on the anatomic development and distribution of the blood supply in the individual case rather than upon the instrument used for the tonsillectomy. The degree of postoperative discomfort and deformity were influenced by the quantity of contiguous muscle tissue removed at the time of operation. The author believes that the removal of small fragmentary fibers of muscle tissue is impossible to avoid and is of no clinical consequence. He concludes that the dissection method "Properly performed and under direct view, step by step, as the tonsil is enucleated, yields the greater number of complete removals."

The Fahraeus Blood-sedimentation Test in Otorhinolaryngology.—It is known that the sedimentation of blood is accelerated under conditions of marked protein disintegration and resorption, as in acute suppurative processes, when the acceleration is in direct ratio to the extension and severity of the inflammation. Applying the Fahraeus test to certain otorhinolaryngologic conditions, BERTOG (*Ztschr. f. Hals-, Nasen- u. Ohrenhlk.*, 1924, **10**, 28) found that in acute suppurative lesions of the middle and external ear, and the accessory sinuses, the rapidity of sedimentation varied from 15 to 75 mm. The technic consisted of filling a 2-cc syringe, containing 0.4 cc of 2.5 per cent sodium citrate solution with blood. After mixing by centrifugalization the citrated blood was drawn into a 1-cc pipette of 3-mm. caliber, allowed to stand and the results read in forty-five or sixty minutes. The author believes the test has a particular field of usefulness in doubtful cases, but stresses the importance of serial tests, inasmuch as a single examination is inadequate because acceleration of sedimentation merely indicates presence of suppuration in the body.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Extensive Necrosis of the Liver in an Infant.—In recent years descriptions of necroses of the liver have commonly appeared in the literature and their incidence appears to be increasing. These liver necroses have largely been associated with infectious diseases and intoxications. In the majority of instances the character of the necrosis is unique and focal. The more extensive necroses, such as

are observed in acute yellow atrophy, have been described in adults as well as in children under a variety of circumstances, of which arsenic poisoning has come into prominence. In children the necroses of liver as they most commonly attract attention have been of small extent and usually associated with various bacterial infections, particularly those arising in the gastrointestinal canal. Acute yellow atrophy has also been described in children, but only occasionally has a severe necrosis been found in infants only a few months old. DEGENER and JAFFE (*Centralbl. f. allg. Path.*, 1925, **35**, 556) report a case in a dead-born male child in which other than the presence of some anasarca and a slight amount of ascites nothing unusual was found in the remaining tissues of the body except the presence of extensive necroses of the liver. This appears to be the only case on record where such a lesion has been found in the newborn. The liver was of usual size and showed nothing other than necroses with a geographical distribution involving mainly the right lobe. These necrotic areas were plainly visible and sharply demarcated from the surrounding and otherwise healthy-looking liver structure. On microscopic examination there appeared to be a slight fibrosis in the liver, but the authors were unable to demonstrate the spirochete in this or other tissues. The authors were unable to determine the cause of the necrosis, although they suggest an undetermined infection. The extent of the necrosis as shown in an illustration suggests further the possibility that there was a marked circulatory disturbance in the liver and that this condition accounted for the necrosis more than the presence of toxins in the blood.

A Note on the Bacteriophage with Respect to Complement-fixation Tests.—Using beef extract bouillon and beef infusion bouillon to immunize rabbits SANDERSON (*Jour. Immunol.*, 1925, **10**, 625) found that the sera of these animals possessed complement-fixing substances displayed in the presence of the homologous or heterologous antigen. He also found that the sera of 3 of 4 untreated rabbits contained this substance in just as high concentration as the sera of the treated rabbits. It was not present in the serum of the fourth rabbit nor in the sera of 4 calves, 1 guinea pig and 1 horse. The serum of a rabbit immunized with a broth culture of Bacillus coli dissolved by the action of a phage showed a comparable concentration of complement-fixing substance but this was demonstrable with either beef extract bouillon or Bacillus coli phage in broth as antigen. Similarly the sera of the untreated rabbits would fix complement using the Bacillus coli phage as antigen though calf serum failed to do so. It is concluded that rabbit serum commonly contains nonspecific complement-fixing substances demonstrable in the presence of bouillon as antigen. Also a possible fallacy in similar experiments of de Herelle which were used to argue for the identity of all bacteriophages, is demonstrated.

Isolation, Morphology and Cultural Reactions of Bacillus Tetani.—FILDES (*Brit. Jour. Exper. Path.*, 1925, **6**, 62) describes a new method for the isolation of Bacillus tetani from mixed cultures and tetanic material. It was noted that Bacillus tetani, under suitable conditions, has a tendency to grow as a spreading, lacy film on the surface of a

medium, this characteristic being much more pronounced than with other anaërobes. Inoculation was made into the water of condensation of a sloped tube of agar, the growth spreading to the apex of the slant in one or two days. Contaminating organisms spread only to a minor extent. Septic blood agar was the medium used. Six specimens of material from human cases of tetanus were studied, and all 6 were found positive. Two hundred specimens of human feces, with 2 positive, 200 specimens of horse feces with 34 positive, and 70 specimens of soil with 33 positive, were the sources of the strains studied. In all, 75 strains positively identified as Bacillus tetani were investigated. The technic of isolation is described. The variation in the morphology of the organism impressed the author, particularly with regard to the spores. He claims that the typical "drumstick" form is idealistic and that the oval spore variously placed is met with under different conditions. A thorough study of the cultural reactions is reported; the opacity in blood broth appearing usually in the second day; indol from all of 70 strains in seven days; characteristics of shake cultures; feeble or absent growth in gelatin; no coagulation of milk; no fermentation of sugars; and evidence is given of a slight proteolytic action of the organism. The strains used have been deposited in the national collection of Type Cultures, Lister Institute, London.

Experimental Soot Cancer.—A method of extracting an active fraction from soot for the production of experimental carcinoma in mice is reported by PASSEY and CARTER-BRAINE (*Jour. Path. and Bact.*, 1925, **28**, 133). Three fractions were prepared, one containing the ether-soluble substances in soot; one containing the ether-soluble bases and neutral substances and the third the ether-soluble bases of the water-soluble salts. Eighty young adult white mice were used in three groups comparable as regards color and size. The skin on the back was depilated and the fractions, diluted with ether were applied with camel's hair brushes, at first three times a week and later twice. Fractions 1 and 3 produced no cancer. Using fraction 2 on the 40 mice in one group, 18 survived until the eighty-eighth day and 16 of these had developed warts. Nine of the 18 showed malignant changes in from six to twelve months. As reported by other workers, initial mortality is high, ulceration, parasitic diseases and toxic states reducing the number of experimental animals about one-half. Protocols are given of each of the 18 animals mentioned. Fraction 2 was now investigated and was further fractioned by distillation in an atmosphere of coal gas into four distillates. By omitting scarification of the depilated skin, malignant tumors were produced by the application of the higher-boiling distillates. The authors conclude that an active-fraction of soot consisting mainly of ether-soluble bases will produce cancer readily in mice and that these carcinogenetic factors are distilled over in the fractions boiling above 190° C.

The in Vitro Cultivation of Tissues with Reference to the Production of Cancer by Means of Radium and Roentgen-rays.—An interesting study of experimental cancer is reported by MOTTRAM (*Brit. Jour. Exper. Pathol.*, 1925, **6**, 53). It has been the custom to look for a stimulating factor in the cause of cancer. This work directs one's

attention to another possibility; that of the destruction of growth-inhibiting factors. Kidneys of rats were emulsified and extracted with Locke's solution at 0° C. Sets of cultures were prepared using plasma, embryo extract, kidney extract and kidney fragment and the cultures were incubated for three days. They were then fixed and stained and the extruded cells and mitoses were counted. It was demonstrated that a growth-inhibiting factor was extracted from old tissues but not from young and not from Jensen's rat sarcoma. Radiation experiments were carried out in vitro and in vivo. For the former, radium was used as the source of radiations. Details of the cultures and technic were given. For the in vivo work, both radium and roentgen ray were used, of which full details are given. In summing up, it was found that extracts made at 0° C. from the kidneys of adult rats inhibit the in vitro growth of kidney cells. Exposure of emulsified kidneys to 35° C. for one or two hours before the extract is made destroys the inhibitory factor. Exposure of emulsified kidneys in vitro to radium and in vitro and vivo to radium and roentgen rays likewise destroys this factor. The radiation effect was immediate and became progressively less as time was allowed to lapse between the radiation and the making of the extract.

Adenomyoma of the Stomach.—Case reports and discussion are presented of 5 cases of adenomyoma of the stomach by STEWART and TAYLOR (*Jour. Pathol. and Bact.*, 1925, **28**, 195). It is considered as a heterotopia closely simulating clinically, a number of other diseases of more frequent occurrence, especially gastroduodenal ulceration. Grossly one finds a localized but ill-defined thickening, both visible and palpable, in the pyloric region of the stomach. From the periteonal aspect the appearance may simulate an early pyloric cancer. The mucous membrane is normal. The cut surface shows whorling of the pyloric musculature with scattered cystic spaces of small size, or solid yellowish areas. The essential feature histologically, is the presence of glandular tissue both differentiated and undifferentiated. Unstriped muscle seems to form an integral part of the tumor. The paper gives minute details of the clinical course, morbid anatomy, histology of the 5 cases and a general discussion of gastro-intestinal heterotopias. The authors indicate that the condition is easily recognized in the gross and that upon identifying it, local excision is adequate treatment. Admirable plates facilitate the reading of the text.

The Incidence of Two Types of Group II Human Red Blood Cells.—KLINE, ECKER and YOUNG (*Jour. Immunol.*, 1925, **10**, 595) confirm the report of Guthrie and Huck, that individuals with Group II blood type may be subdivided into those whose cells contain agglutinogen B and those whose cells contain agglutinogens B and C. By absorbing Group III serum with Group II cells containing only B, the serum was found to still promptly agglutinate the cells of 81 per cent of 200 Group II adults and the cells obtained from the umbilical cord of 51 per cent of 100 Group II newborn infants. It is concluded that the Group II cells which failed to agglutinate in the absorbed serum contained only agglutinogen B while those which agglutinated contained agglutinogens B and C. The authors suggest that the agglutinogen C is identical with the agglutinogen X of Coca and Klein.

Innervation as a Factor in the Experimental Production of Cancer.—CRAMER (*Brit. Jour. Exper. Pathol.*, 1925, **6**, 71) reports a study of 43 mice on which skin-autoplast or skinflap operations had been done. In one series an oblong piece of skin was completely removed from the back and then carefully stitched on again; and in another the flap was left connected with the unsevered skin by a narrow bridge. When healing was complete, after unsuccessful operations had been discarded, tar-painting was begun twice weekly in the center of the denervated area and on an area of normal skin. At the end of nine months, 12 of the surviving mice had developed tumors and 5 had remained negative. All 12 had tumors on the normal skin; 5 had also developed tumors on the denervated area. It is presumed that after two or three months, innervation of the denervated areas has taken place. Different areas of normal skin showed different susceptibilities to the tar-painting. The study shows that the presence of an efficient nervous control is an important factor in the process of chronic irritation leading to cancer formation. One cannot define as yet the part played by the nervous control.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Some Effects of High Environmental Temperatures on the Organism.—FLINN (*Pub. Health Repts.*, 1925, **40**, 868) undertook his investigations to obtain a more intimate knowledge of the specific effects of high environmental temperature upon the individual organs and tissues of the body so that the more general effects as observed among men who are compelled to work where the air temperature is abnormally high could be more intelligently interpreted than has heretofore been possible. The following summary is given: "(1) During an exposure of six hours to an environmental temperature of 20° or 30° C. there was a drop in body temperature, probably due to a decrease in muscular activity. At 40° C. there was an increase of 1° in body temperature without an initial drop. At 45° and 50° C. the body temperature rose within an hour to such a height that it was deemed unsafe to continue the experiments. (2) The oxygen capacity of the blood showed no changes during the exposure to the different temperatures that cannot be accounted for by the diurnal changes in the hemoglobin or the concentration of the blood due to excessive evaporation of water. (3) The oxygen content of the blood remained

unchanged at 20° C., but showed a drop at 30° C., which is probably associated with the low rate of metabolism at this temperature. At 45° and 50° C. there is a slight increase in the oxygen content, due to the increased aëration of the blood at these temperatures; but this increase is not in direct proportion to the increased passage of air over the membranes of the mouth and throat. (4) At temperatures of 20° and 30° C. the alkali reserve remains unchanged, while at 40° C. there is a sharp fall during the first four hours, followed by a slower fall during the next two hours. At temperatures of 45° and 50° C. there is a rapid depletion of the alkali reserve from the beginning, which is almost identical for each of these two temperatures. (5) The carbon-dioxid content follows the alkali reserve, except that at 30° C. there is a slight rise for the same reason that the oxygen content falls. (6) The hydrogen-ion concentration of the plasma remains unchanged during an exposure of the animal to a temperature of 20° C., 30° and 40° C., but decreases at temperatures of 45° and 50° C., due to the excessive pulmonary ventilation at those temperatures with the consequent washing out of carbon dioxid without a compensatory loss of alkali from the blood. (7) The concentration of blood sugar falls during an exposure to temperatures of 20° and 30° C. This fall is probable associated with inactivity of the animal during the course of the experiment. At 40° C. it falls during the first two hours to increase during the following four hours. At 45° C. no change was noted during an hour's exposure, while at 50° C. there was a sharp rise during this time. (8) The blood solids at 20° and 30° C. showed only the usual diurenal changes. At 40°, 45° and 50° C. the concentration of the blood increases with the environmental temperature, no initial drop being seen. (9) An increased air movement benefits the organism by laying the deleterious effects, but apparently at the expense of the organism itself. (10) The free drinking of water during an exposure to high air temperature is of greatest benefit in maintaining the organism in a normal condition."

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